NUPLAZID™

(pimavanserin)

SPONSOR BACKGROUND INFORMATION FOR A MEETING OF THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE ON 29 MARCH 2016

ACADIA Pharmaceuticals Inc.

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Abbreviations and Acronyms

5-HT	5-hydroxytryptamine (serotonin)
AC-279	*N*-desmethyl-pimavanserin, major metabolite
ACP-103	pimavanserin tartrate
ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
All-PIM	all subjects treated with pimavanserin regardless of dose within the PDP6 Population
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{0-t}	area under the plasma concentration-time curve from time 0 to time of last detectable concentration at time t
BMI	body mass index
BOCF	baseline observation carried forward
BPST-PD	brief psychosocial therapy for Parkinson's disease
CBS	Caregiver Burden Scale
CDF	cumulative distribution function
CGI-I	Clinical Global Impression scale – Improvement
CGI-S	Clinical Global Impression scale – Severity
CI	confidence interval
CL/F	oral clearance
C_{max}	maximum plasma concentration
Cp	plasma concentration
CYP	cytochrome P450
ECG	electrocardiogram
EPS	extrapyramidal symptom
FDA	Food and Drug Administration
GSAPS-H+D	sum of the scores of the global items for each of the Hallucinations

	and Delusions domains of the SAPS
hERG	human ether-à-go-go related gene
IC_{50}	half maximal inhibitory concentration
IND	Investigational New Drug
LOCF	last observation carried forward
LS	least squares
LSM	least squares mean
MAR	missing at random
mITT	modified intent-to-treat
MMRM	mixed-effect model repeated measure
MMSE	Mini-Mental State Examination
MNAR	missing not at random
NDA	New Drug Application
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NOEL	no-observed-effect-level
NPI	Neuropsychiatric Inventory
NPI-H+D	Neuropsychiatric Inventory hallucinations and delusions subscales
OC	observed cases
PBO	placebo
PD	Parkinson's disease
PDP	Parkinson's disease psychosis
PDP4	PDP subject analysis population treated with pimavanserin for 4 weeks
PDP6	PDP subject analysis population treated with pimavanserin for 6 weeks
PDPLT	PDP subject analysis population treated with pimavanserin in open-label, long-term studies
PIM	as a general label – pimavanserin
PK	pharmacokinetic
PMM	pattern mixture model
PR interval	the portion of the electrocardiogram between the onset of the P wave and the QRS complex
QRS interval	QRS interval of ECG

QTc	QT interval corrected for heart rate of ECG
QTcF	corrected QT interval using Fridericia's correction method
QTcI	individualized corrected QT interval
R-SAT™	Receptor Selection and Amplification
SAE	serious adverse event
SAPS	Scale for the Assessment of Positive Symptoms
SAPS-D	SAPS-Delusions subscale
SAPS-H	SAPS-Hallucinations subscale
SAPS-H+D	SAPS-Hallucinations and Delusions subscales
SAPS-PD	SAPS in Parkinson's Disease
SCOPA	Scales for Outcomes in Parkinson's Disease
SCOPA-DS	Scales for outcomes in Parkinson's disease – Daytime sleep
SCOPA-NS	Scales for outcomes in Parkinson's disease – Nighttime sleep
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
$t_{½}$	terminal plasma half-life
T_{max}	time to maximum plasma concentration
TQT	thorough QT
ULN	upper limit of normal
UPDRS	Unified Parkinson's Disease Rating Scale
UPDRS Parts II+III	Unified Parkinson's Disease Rating Scale Parts II+III
US PSG	US Parkinson Study Group
USP	US Pharmacopeia
UTI	urinary tract infection
WBC	white blood cell count
WOCF	worst observation carried forward

Style Conventions

Within this document study numbers have been abbreviated from the form "Study ACP-103-006" to "Study 006" or just “006.”

In addition, "pimavanserin" is abbreviated to "PIM" in some column headings of tables and within the name of some analysis populations. The abbreviation "PBO" is used in table headings for "placebo."

Doses of pimavanserin tartrate are generally referred to as "pimavanserin" -- the reader should note that a dose of 34 mg pimavanserin is equivalent to 40 mg of the salt form, pimavanserin tartrate. Final labeling is required to reflect the new USP salt policy and will describe the proposed pharmacologic dose of pimavanserin as 34 mg (based on the active moiety). The briefing document will also cite doses used during the development program according to dose based on the active moiety.

Subjects in the 012, 014, and 020 studies received 42 days (6 weeks) of treatment. The end-of-treatment visit in the Phase 3 studies was referred to as Day 42 in 012 and 014 and Day 43 in 020. The treatment period in Studies 012, 014, and 020 is therefore generally referred to as “6 weeks” and the Day 42 or 43 study visit as the “Week 6” visit.

The term “effect size” is used repeatedly in the document. It refers to Cohen’s *d*.

1 Executive Summary

NUPLAZID™ (pimavanserin) is a selective inverse agonist of the 5-hydroxytryptamine 2A (5-HT_{2A}) receptor being developed for treatment of Parkinson's disease psychosis (PD psychosis). The pharmacologic profile of pimavanserin is unique in that this drug preferentially targets the 5-HT_{2A} receptor subtype, has low activity at the 5-HT_{2C} receptor, and shows no measurable activity at other serotonergic, dopaminergic, histaminergic, adrenergic, or muscarinic receptors. This mechanism of action is particularly beneficial for PD patients because it does not block dopamine or worsen motor symptoms of PD.

Pimavanserin is under review for the indication of the treatment of psychosis associated with Parkinson's disease. The recommended dose is 34 mg once daily. It is the first compound submitted for this indication and has been granted breakthrough designation and priority review by the Food and Drug Administration (FDA).

Parkinson's Disease Psychosis

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting about one million people in the United States. While PD has been traditionally defined on the basis of motor features, including resting tremor, bradykinesia, rigidity, and disturbances of balance and posture, patients with PD also experience a number of nonmotor symptoms that are highly prevalent and often have a greater impact on patient disability and quality of life. Psychotic symptoms are common in PD and affect more than 50% of patients at some point during the course of their disease. The hallmark symptoms of PD psychosis are hallucinations and delusions that typically increase in frequency and severity over time. PD psychosis is associated with poorer patient quality of life and increased patient morbidity, hospitalization, nursing home placement, and mortality as well as increased caregiver distress and burden. In fact, PD psychosis has been referred to as the single greatest stressor for caregivers and a leading reason for nursing home placement of PD patients. There are currently no FDA-approved treatments for PD psychosis.

Current evidence suggests that PDP is not merely a complication of dopaminergic drug use, but, rather, involves factors both extrinsic and intrinsic to the disease. To date, the management of PD psychosis is limited to identifying and treating the underlying systemic illnesses, minimizing polypharmacy, utilizing nonpharmacologic interventions, and/or reducing dopaminergic therapy. Altering dopaminergic PD medication regimens can be a balancing act in which psychotic symptoms may improve at the cost of worsening motor symptoms. Moreover, when adjustment of PD medications is ineffective or not tolerated, physicians resort to the off-label use of currently available antipsychotics, particularly as PD psychosis becomes more severe and disabling. However, currently used antipsychotic medications are antagonists at the dopamine D_2 receptor, and therefore negatively impact

motor function. In addition, antipsychotics, other than clozapine, have not demonstrated efficacy in the controlled PD Psychosis clinical trials and clozapine imposes extensive monitoring burden due to safety requirements. Thus, PD psychosis presents a significant treatment challenge due to the lack of a safe, effective, and approved pharmacologic agent.

Considering the chronic, progressive nature of PD psychosis and its high incidence and burden, a therapeutic intervention is urgently warranted to effectively manage psychotic symptoms in PD patients. Importantly, such a treatment should manage the symptoms of PD psychosis without exacerbating underlying parkinsonism, accelerating cognitive decline, or increasing the risk for sedation or other adverse events that currently limit the use of antipsychotics.

Development Program

Pimavanserin is a highly selective and potent inverse agonist for the 5-HT_{2A} receptor. The unique structural characteristics and pharmacological selectivity profile of pimavanserin differentiates it from typical and atypical antipsychotics. Specifically, pimavanserin does not exhibit measurable activity at the dopaminergic, histaminergic, adrenergic, or muscarinic receptors that are individually or collectively associated with significant dose-limiting side effects of other antipsychotic drugs. In preclinical studies pimavanserin appeared to be generally well tolerated. A finding of lung pleural/subpleural fibrosis and chronic inflammation, considered secondary to phospholipidosis, was observed in rats at the end of a 6-month recovery phase of a 6-month rat oral toxicity study. This finding is histologically different from chronic interstitial lung disease caused by directly acting lung toxicants. The observed lung pleural/subpleural fibrosis and chronic inflammation occurred at doses that exceeded the maximum tolerated dose and at exposures that were 18- and 10-fold, respectively, the intended human exposure (based on AUC). This observation is considered unlikely to be relevant to the clinical use of pimavanserin.

In humans pimavanserin is orally bioavailable, readily crosses the blood-brain barrier, and is extensively metabolized, predominantly in the liver. Because the metabolism of pimavanserin is affected by strong cytochrome P450 (CYP) 3A4 enzyme (CYP3A4) inhibitors, which results in an increase in maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of approximately 3-fold, a dose reduction is recommended when co-administering pimavanserin with moderate to strong CYP3A4 inhibitors. Pimavanserin does not affect metabolism of CYP3A4 substrate drugs, has no effect on coadministered carbidopa/levodopa, and its bioavailability is unaffected by a high-calorie or high-fat meal. The apparent plasma elimination half-life ($t_{½}$) of pimavanserin is about 57 hours and steady state is achieved in 12 days (5 half-lives) of once-daily dosing.

The clinical development program in PD psychosis has further evolved through early clinical trials and regulatory consultations with the Agency seeking alignment on the key design elements, endpoints and the overall submission requirements. To date, the pimavanserin clinical development program involves 25 studies (completed or ongoing), with the following key trials:

- 4 placebo-controlled, short-term studies in PD psychosis subjects
    - Initial Phase 2 proof-of-concept Study 006
    - Phase 2b/3 Studies 012 and 014
    - Pivotal Phase 3 Study 020
- 2 open-label extension studies
    - Studies 010 and 015

Over the course of these studies, over 1200 subjects have received pimavanserin. These include 616 PD psychosis subjects. Across all populations and indications studied, a total of 764 subjects have received pimavanserin 34 mg, dose proposed as therapeutic dose in PD psychosis. From controlled studies in PD psychosis, 498 subjects continued in long-term extension studies, and more than 250 subjects have received treatment for over a 1 year and more than 150 subjects for over 2 years.

Efficacy Results

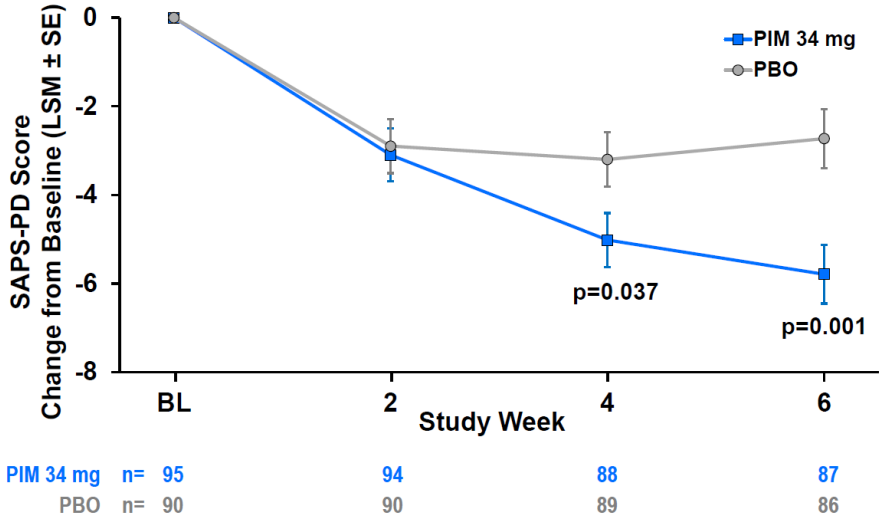
The initial Phase 2 proof-of-concept Study 006 was a double-blind, randomized, multicenter, dose-escalation study of 4 weeks duration involving 60 subjects with PD psychosis. The primary endpoint in this trial was met, demonstrating that doses up to 51 mg of pimavanserin were well tolerated and did not worsen motor control in PD psychosis subjects. In addition, numerically greater improvements in psychosis scores were observed in the pimavanserin group compared with the placebo group. Based on the Phase 2 data, a Phase 2b/3 program with two almost identical studies (012 and 014) was initiated in 2007. The first study, 012, was completed in 2009. However, in this study pimavanserin did not statistically separate from placebo on the primary endpoint for psychosis. Despite this outcome, a signal of efficacy was observed at the 34 mg dose in US centers. In US centers central, independent raters providing assessments via live video feed were used. Outside of the US ratings were performed by site raters. On the basis of the overall results of Study 012, Study 014 was stopped early as this study tested lower pimavanserin doses, and had the same study design as Study 012.

Close examination of the study design of Studies 012 and 014 identified a number of strategies that were implemented to improve the design and operational conduct of the pivotal Phase 3 Study 020. This study was initiated in 2010 following discussions with the

FDA to gain agreement on these design changes and refinements that were intended to better control overall variability and placebo response. Some key design changes included the utilization of central independent raters, two treatment arms and the Parkinson's disease-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD) to evaluate the primary endpoint.

Using a randomized, double-blind, placebo-controlled, outpatient study design, Study 020 evaluated the safety and efficacy of daily pimavanserin 34 mg dose compared with placebo over a 6-week treatment period in 199 subjects with moderate to severe PD psychosis. For the primary endpoint (i.e., reduction from baseline in the SAPS-PD score), the pimavanserin arm achieved a mean improvement of 5.79 points compared with 2.73 points for placebo, thus providing a clinically meaningful difference of 3.06 points between the 2 arms at Week 6 (Figure 1–1). This difference translated to an effect size of 0.5. While both groups showed similar improvement at Week 2, by Week 4, statistical separation had been achieved, and the difference between the 34 mg pimavanserin and placebo arms continued to increase until the end of the study at Week 6.

Figure 1–1 Primary Endpoint (SAPS-PD): Change from Baseline (Study 020; mITT, MMRM, N=185)



Note that in the SAPS-PD, a negative change in score indicates improvement, whereas a positive change in score indicates worsening of symptoms.
Abbreviations: SAPS-PD = Parkinson's disease-adapted Scale for the Assessment of Positive Symptoms; LSM = least squares method; SE = standard error; BL = baseline; PIM = pimavanserin; PBO = placebo; mITT = modified intent to treat; MMRM = mixed model repeated measures

A number of sensitivity analyses were conducted to assess the impact of missing data on the primary SAPS-PD endpoint. All analyses showed a significant improvement in psychosis for pimavanserin over placebo, indicating that the results were robust with alternative imputation methods.

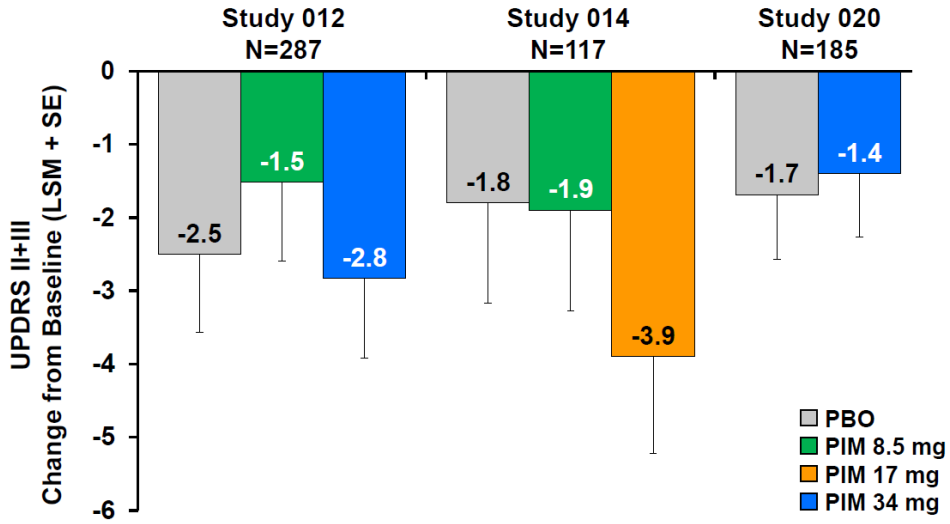
For the secondary endpoints, pimavanserin-treated subjects also showed significant mean improvement on the investigator-assessed Clinical Global Impressions (CGI) scales: the CGI-S (overall severity) and CGI-I (overall improvement) compared with subjects receiving placebo.

The clinical significance of this treatment effect is particularly evident in responder analyses:

- A SAPS-PD complete response (i.e., a score of zero, indication the absence of symptoms), was achieved by 12% of pimavanserin-treated patients compared to 1% of placebo-treated patients (p=0.002).
- The proportion of patients who were either much improved or very much improved on the CGI-I was significantly greater in the pimavanserin group compared to placebo (41% vs. 23%, p=0.008).

In addition, on the key secondary endpoint, the Unified Parkinson's Disease Rating Scale Parts II+III (UPDRS Parts II+III) was used to assess potential adverse effects of pimavanserin on motor symptoms of PD. In the UPDRS, a negative change in score indicates improvement, whereas a positive change in score indicates worsening of symptoms. Consistent with the results of the previous studies (012, 014, and 006), in the Study 020 pimavanserin did not worsen motor control as evidenced by demonstrating non-inferiority to placebo on the UPDRS Parts II+III scale (Figure 1–2).

Figure 1–2 Secondary Endpoint: Change from Baseline in UPDRS Parts II+III



Least square means (LSM) and standard errors (SE) from ANCOVA model with treatment and region (Studies 012 and 014) as factors and baseline as a covariate at Week 6 (Studies 012, 014, and 020).
Abbreviations: UPDRS = Unified Parkinson's Disease Rating Scale; LSM = least square means; SE = standard error; PIM = pimavanserin; PBO = placebo

For the exploratory endpoints, pimavanserin demonstrated significant improvements on evaluations of nighttime sleep quality (SCOPA-NS) and daytime sleepiness (SCOPA-DS) at

Week 6. These benefits are particularly important because sleep disturbance is a major problem for patients with PD psychosis, and poor sleep quality in PD patients can exacerbate psychotic symptoms and worsen cognitive functioning, and contributes to increased burden of illness. Additionally, on the 22-item Zarit Caregiver Burden Scale pimavanserin demonstrated significant improvement compared to placebo.

Thus, efficacy data from the pimavanserin clinical program supports the conclusion that pimavanserin at the once-daily dose of 34 mg is effective in treating psychotic symptoms in PD. The robustness of the efficacy data of pimavanserin from Study 020 is strongly supported by substantial effect size, persuasive statistical evidence, confirmatory sensitivity analyses, and consistency of results across measures and assessors. Data from Studies 012 and 014 provide additional supportive information for pimavanserin efficacy. Importantly, across all studies the beneficial effects have been achieved without negatively affecting motor function.

Safety Results

The safety of pimavanserin was evaluated across the 6-week studies, including Studies 012, 014, and 020, with daily exposures of 8.5, 17, and 34 mg of pimavanserin compared with placebo. Overall, treatment-emergent adverse events (TEAEs) were reported at similar rates across the different arms. In Studies 012 and 020, the events occurring with a 2% or greater difference in the pimavanserin-treated subjects compared with placebo were nausea, peripheral edema, confusion, and hallucination. Events occurring in subjects receiving placebo with a 2% or greater difference compared with pimavanserin were falls, headache, and orthostatic hypotension (Table 1–1).

Table 1–1 Common Treatment Emergent Adverse Events ≥5% in Either Treatment Group (PDP6 Population)

Preferred Term	Subjects, n (%) Placebo	
	34 mg (N=202) n (%)	Placebo (N=231) n (%)
Overall	**124 (61.4)**	**141 (61.0)**
Urinary tract infection	15 (7.4)	16 (6.9)
Nausea	14 (6.9)	10 (4.3)
Oedema peripheral	14 (6.9)	5 (2.2)
Fall	13 (6.4)	21 (9.1)
Confusional state	12 (5.9)	6 (2.6)
Hallucination	10 (5.0)	7 (3.0)
Headache	5 (2.5)	12 (5.2)
Orthostatic hypotension	2 (1.0)	12 (5.2)

Table entries include Studies 012 and 020 mg vs. placebo.

During the clinical trials, no notable effects in laboratory values, vital signs, or neurological measures were noted. Importantly, the data across all the controlled studies showed that the safety concerns commonly associated with antipsychotics, such as orthostatic hypotension, metabolic disorders, motor impairment and sedation, were either not observed or occurred at a lower frequency with pimavanserin compared with placebo in the controlled studies.

An overall increase in serious adverse events (SAEs) for patients treated with pimavanserin compared to placebo has been observed in pimavanserin controlled studies. A careful review of these events did not reveal common underlying mechanism related to the study drug, or a recurring pattern behind this observation. Five deaths were noted in the controlled studies: one in the 8.5 mg dose group, three in the 34 mg group, and one in the placebo group; there were no deaths reported in the 17 mg group. The small numbers of reported events makes it difficult to reliably assess association with pimavanserin treatment. A review of the observed mortality suggested a pattern consistent with medical comorbidities and risk factors associated with the background disease. ACADIA is committed to continued active surveillance and evaluation of these events through risk management and pharmacovigilance programs.

Additional safety findings noted over the course of the pimavanserin clinical program include a mild-moderate QTc interval prolongation observed in the thorough QT Study and the Phase 3 trials. This can be managed through labeling and physician education as is commonly done for other drugs that cause a similar degree of QTc prolongation. Also, pimavanserin exposure increases when pimavanserin is concomitantly administered with a moderate or strong CYP3A4 inhibitor. The proposed pimavanserin prescribing information recommends that the dose be reduced to 17 mg (i.e., a 50% dose reduction) when taken with a potent CYP3A4 inhibitor.

Conclusion

In summary, with its highly targeted and selective receptor binding profile, pimavanserin provides a promising approach to the treatment of psychosis in PD, a condition that clearly lacks effective treatment options. Pimavanserin provides clinically meaningful benefit, with robust improvements observed across multiple measures of psychosis that were achieved without causing adverse effects on motor function. Pimavanserin demonstrated an acceptable tolerability profile and well characterized safety risks that can be appropriately managed through labeling and pharmacovigilance programs. The totality of data support the conclusion that the benefits of pimavanserin treatment outweigh the potential risks. Pimavanserin can provide a valuable treatment option for patients experiencing psychotic symptoms associated with Parkinson's disease.

2 Pimavanserin for the Treatment of Parkinson's Disease Psychosis

A New Drug Application (NDA) for NUPLAZID™ (pimavanserin) was submitted by ACADIA Pharmaceuticals Inc. (ACADIA) for the treatment of psychosis associated with Parkinson's disease on 01 September 2015. Specifically, the proposed indication is as follows:

NUPLAZID is indicated for the treatment of psychosis associated with Parkinson's disease.

The recommended therapeutic dose of pimavanserin is 34 mg.

This briefing document has been prepared by ACADIA to provide Sponsor background information relevant to the meeting of the Psychopharmacologic Drugs Advisory Committee scheduled for 29 March 2016.

3 Parkinson's Disease Psychosis: Significant Unmet Medical Need

3.1 Parkinson's Disease and Associated Psychosis

Parkinson's disease (PD) is a progressive neurodegenerative disorder. According to the Parkinson's Disease Foundation, about 1 million people in the United States (US) and about 7 to 10 million people worldwide suffer from the disease (Parkinson's Disease Foundation 2016). PD has been traditionally defined on the basis of motor features, including resting tremor, bradykinesia, rigidity, and disturbances of balance and posture; however, patients with PD also experience a number of nonmotor symptoms that are highly prevalent and often have a greater impact on patient disability and quality of life (Fernandez 2012). Nonmotor symptoms can be categorized in 5 domains: cognitive dysfunction, neuropsychiatric, autonomic, sleep, and other nonmotor or sensory (Bernal-Pacheco et al., 2012). The neuropsychiatric domain includes psychosis, in which symptoms may range from mild visual illusions to fully formed systemized hallucinations and delusions (Goldman and Holden 2014). Parkinson's psychosis is associated with poorer quality of life, and increased morbidity, caregiver burden, and nursing home placement. Despite the high prevalence and debilitating impact, PD psychosis patients do not receive appropriate treatment, owing to lack of an effective, safe, and approved therapy (Hermanowicz and Edwards 2015).

3.2 Parkinson's Disease Psychosis Prevalence, Evaluation, and Symptomatology

Over 50% of PD patients experience PD-related psychotic symptoms during the course of their disease (Forsaa et al., 2010). Current evidence suggests that PD psychosis is not merely a complication of dopaminergic drug use, but, rather, involves factors both extrinsic and intrinsic to the disease, such as PD duration and severity (Zahodne and Fernandez 2010). PD psychosis is distinct from other psychotic disorders. Schizophrenia and schizoaffective disorder, for example, are differentiated from PD psychosis by the onset of psychotic symptoms in late adolescence and early adulthood; in dementia with Lewy bodies, the temporal course differs from that in PD psychosis (Ravina et al. 2007). PD psychosis can be diagnosed based on criteria outlined by the National Institute of Neurological Disorders and Stroke (NINDS) and National Institute of Mental Health (NIMH) Work Group (Table 3–1) (Ravina et al., 2007).

Table 3–1 Diagnostic Criteria for PD Psychosis Proposed by the NINDS and NIMH Work Group

Characteristic symptoms (Criterion A)	Presence of at least one of the following symptoms (specify which of the symptoms fulfill the criteria): Illusions False sense of presence Hallucinations Delusions
Primary diagnosis	United Kingdom brain bank criteria for PD
Chronology of the onset of symptoms of psychosis	The symptoms in Criterion A occur after the onset of PD
Duration	The symptom(s) in Criterion A are recurrent or continuous for 1 month
Exclusion of other causes	The symptoms in Criterion A are not better accounted for by another cause of parkinsonism such as dementia with Lewy bodies, psychiatric disorders such as schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features, or a general medical condition including delirium
Associated features: (specify if associated)	- with/without insight - with/without dementia - with/without treatment for PD (specify drug, surgical, other)

Abbreviations: NINDS = National Institute of Neurological Disorders and Stroke; NIMH = National Institute of Mental Health; PD = Parkinson's disease
Source: Ravina et al., 2007

The most common symptom of PD psychosis is visual hallucinations, occurring in up to one third of patients with PD (Goldman and Holden 2014). Auditory, olfactory, and tactile hallucinations are less common than visual hallucinations but do occur often in parallel with visual hallucinations. Hallucinations can sometimes be described as "benign"; however, with PD progression and increased cognitive deficits, threatening hallucinations become more prominent as insight is lost and salience is compromised. In general, hallucinatory symptoms tend to last for a few seconds to a few minutes, and the frequency can vary. In more severe cases, the symptoms may occur several times a day. Delusions are less common, occurring in about 5% to 10% of PD patients, and are generally characterized as paranoid or jealous (Goldman and Holden 2014). Common recurring themes include spousal infidelity or fear of harm from unidentified people or even those providing care to the patient. Misidentification syndromes have also been reported in patients with PD psychosis. The phenomenology and examples of PD psychosis are elaborated in Table 3–2.

Table 3–2 Phenomenology and Examples of PD Psychosis

Illusions	Misperceiving or misinterpreting an object really present mistaking a lamp-post for a person or a chair for a dog
Presence hallucinations	Feeling that someone or a shadow is close by
Passage hallucinations	Experiencing fleeting images in the visual periphery
Simple hallucinations	Seeing flashes of light, colors, lines, patterns
Complex hallucinations	Seeing formed images of people (little children at play; distorted figures; deceased relatives), animals (small furry animals running around), objects; Hearing music and voices
Multi-modal hallucinations	Having hallucinations in more than modality: visual, auditory, tactile, and/or olfactory; most common visual plus auditory modalities
Delusions	Having false beliefs; for example, that someone is unfaithful or may harm them (infidelity, paranoia)
Misidentification syndromes	Capgras syndrome: thinking that one's spouse is an imposter; Fregoli syndrome: thinking that familiar people are disguised as strangers

Source: Goldman and Holden 2014

3.3 Impact of Parkinson's Disease Psychosis on Patient Morbidity

Psychotic symptoms contribute substantially to the burden of PD (Goldman and Holden 2014). In a recent study of 492 patients with PD, all neuropsychiatric symptoms, including PD psychosis, had a moderate to large effect on patient quality of life as measured by the Parkinson's Disease Questionnaire Short Form (Alvarado-Bolaños et al., 2015). Correlation coefficients ranged from 0.17 to 0.63 between neuropsychiatric symptoms and quality of life ($p<0.001$). A study conducted in 49 PD patients reported that after controlling for the effects of motor symptoms, the presence of hallucinations predicted poorer quality of life (McKinlay et al., 2008). Among the domains of the Parkinson's disease questionnaire, presence of hallucinations had a significant impact in the domains of activities of daily living, emotional well-being, cognitive impairment, and bodily discomfort (McKinlay et al., 2008).

The symptoms of PD psychosis tend to recur and worsen over time (Zahodne and Fernandez 2010). The Unified Parkinson's Disease Rating Scale (UPDRS) thought disorder subscale was used to identify and measure the continuum of psychotic symptoms through the stages of PD (based on Hoehn and Yahr score) in 235 patients with PD (Aarsland et al., 1999). The severity of symptoms from vivid dreams (1 on the thought-disorder subscale) to hallucinations (2 on the thought-disorder subscale) to delusions (3 and 4 on the thought-disorder subscale) was clearly associated with advancing disease. Vivid dreams have been associated with treatment with levodopa, a dopamine mimetic agent; however, no clear relationship between levodopa dose and psychotic symptom progression has been substantiated in the literature (Klein et al., 1997; Goetz et al., 1998; Holroyd et al., 2001; Merims et al., 2004; Fenelon et al., 2006).

Older age, longer PD duration, worse motor symptom severity; and presence of sleep disorders, depression, autonomic impairment, and dementia have been identified as risk factors for PD psychosis (Goldman and Holden 2014). Among these risk factors, sleep disorders have a substantial impact on quality of life (Quelhas 2013; Jahan et al., 2009). The prevalence of sleep disturbances in PD patients has been reported to be almost 100% (Lees et al., 1988; Poryazova and Zachariev 2005), including both nocturnal sleep disruption and excessive daytime sleepiness (Jahan et al., 2009; Thorpy 2004). Excessive daytime sleepiness may result in part from disturbed nighttime sleep and occurs in about 15% to 20% of PD patients, depending upon motor symptoms, functional impairment, and levodopa dosage (Thorpy 2004). Poor sleep quality exacerbates psychotic behavior and contributes to increased PD psychosis burden (Gama et al., 2015; Melamed et al., 1999; Quelhas 2013).

3.4 Impact of Parkinson's Disease Psychosis on Caregivers

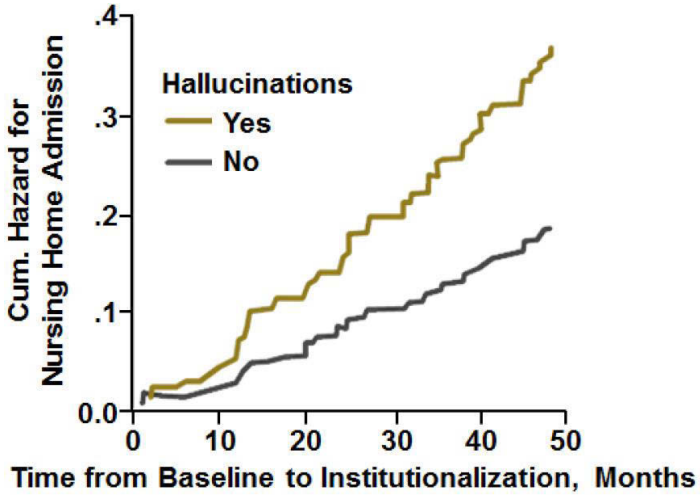
The onset of psychosis marks a milestone in the progression of PD, contributing not only to significant deterioration in quality of life for patients, but imposing substantial burden on caregivers. In patients with delusions, the climate of distrust and unfounded accusations often spirals into an intolerable care situation for both the patient and caregiver. PD psychosis has been referred to as the single greatest stressor for caregivers of PD patients (Zahodne and Fernandez 2010). A number of studies have evaluated predictors of caregiver distress in PD, and psychosis is commonly cited as having the most impact, even when compared with other nonmotor and motor symptoms of PD (Schrag et al., 2006; Aarsland and Karlsen, 1999; Marsh et al., 2004; Leiknes et al., 2015). As for other chronic illnesses, caring for a patient with PD psychosis can cause persistent and progressive social and emotional stress for caregivers, especially as the disease advances and advances and patient disability increases (Carter et al., 2008; O'Reilly et al., 1996). As PD psychosis symptoms worsen, sometimes in association with cognitive decline (Factor et al., 2003; Sanchez-Ramos et al., 1996), the emotional and physical health of caregivers further deteriorates (Schrag et al., 2006), compromising their ability to care for the patient at home (Goetz and Stebbins 1993; Melamed et al., 1999).

3.5 Impact of Parkinson's Disease Psychosis on Nursing Home Placement

Parkinson's disease psychosis is a leading reason for nursing home placement of PD patients (Zahodne and Fernandez 2010). A 4-year prospective study of 178 community-dwelling PD patients in Norway reported hallucinations as one of the main independent predictors of nursing home placement for PD patients (Figure 3–1) (Aarsland et al., 2000). In fact, the presence of psychotic symptoms has been identified in several studies as a significant risk factor for nursing home placement in PD (Factor et al., 2003; Goetz and Stebbins 1993), and more than 40% of PD patients are placed in a nursing home within 2 years of the onset of

psychosis (Factor et al., 2003). Furthermore, residence in nursing homes is often permanent for patients with PD psychosis; relatively few ever return to pre-PD psychosis living (Goetz and Stebbins 1995; Isaacson 2015).

Figure 3–1 Impact of PD Psychosis on Nursing Home Placement



Abbreviations: Cum = cumulative
Source: Aarsland et al., 2000

3.6 Management of Parkinson's Disease Psychosis

No drugs have been approved by the Food and Drug Administration (FDA) for the indication of PD psychosis. The current management approach is limited to adjusting dopaminergic therapy and/or off-label use of low doses of antipsychotics (Ballard et al., 2015; Goldman and Holden 2014). Adjustment of dopaminergic treatment has been considered a guiding principle when psychotic symptoms first present in PD patients (Goldman and Holden 2014). The recommendation is to first wean or stop monoamine oxidase B inhibitors, then amantadine, followed by dopamine agonists and catechol-*O*-methyltransferase inhibitors, and last, reduce levodopa doses. Altering PD medication regimens can be a balancing act, however: psychotic symptoms may improve at the cost of worsening motor symptoms.

In cases where adjustment of PD medications is ineffective or not tolerated, physicians may resort to the off-label use of currently available antipsychotics, particularly as symptoms become more severe and disabling (Goldman and Holden 2014). Presently, antipsychotics used off-label to manage the psychotic manifestations of PD are antagonists at the dopamine D2 receptor, with most also targeting the serotonin receptor, and have not been approved by the FDA in this patient population. In general, there is limited evidence from clinical studies to date to warrant use of these agents for the treatment of PD psychosis. Only clozapine, quetiapine, and olanzapine have been assessed in randomized clinical trials in PD; these trials have several limitations, however, including small patient populations (generally

<50 patients), short duration (4 to 12 weeks), incomplete reporting of adverse events, and exclusion of mortality as an outcome in most cases (Table 3–3).

Table 3–3 Summary of Safety Outcomes from Key Randomized Controlled Trials of Current Antipsychotics for PD Psychosis

Study	Patients	Duration	Key Outcomes
Quetiapine			
Ondo et al., 2005	N=31 quetiapine 100-200 mg, n=21 placebo, n=10	12 weeks	Minimal safety information reported. 2 deaths in placebo group, none in quetiapine group. 4 dropouts in quetiapine (2 serious unrelated illness, 1 lack of effect, 1 poor compliance) vs. 2 in placebo (unrelated serious illness, both resulting in death). Sedation (9 vs. 4) and worsening PD (4 vs. 0) more common in quetiapine group.
Rabey et al., 2007	N=58 quetiapine mean dose 119 mg, n=30 placebo, n=28	12 weeks	1 sudden death in placebo group, no deaths in quetiapine group. Somnolence (7 vs. 2) and urinary tract infection (3 vs. 1) more common in quetiapine group. Cerebrovascular events not described.
Shotbolt et al., 2009	N=24 quetiapine mean dose 72 mg, n=11 placebo, n=13	12 weeks	No description of mortality or individual major adverse events. 3 dropouts in each group due to tolerability
Kurlan et al., 2007	N=40 quetiapine mean dose 120 mg, n=20 placebo, n=20	10 weeks	Mortality not specifically described. Vascular events 3 quetiapine vs. 0 placebo.
Fernandez et al., 2009	N=16 quetiapine mean dose58.3 mg, n=8 placebo, n=8	4 weeks	No description of mortality or cerebrovascular events. Drowsiness 3 quetiapine vs. 1 placebo. Worsening parkinsonism 3 quetiapine vs. 0 placebo.
Clozapine			
French Clozapine Group, 1999	N=60 clozapine mean dose 36 mg, n=32 placebo, n=28	4 weeks	Mortality and cerebrovascular adverse events not described. Worsening parkinsonism 7 clozapine vs. 0 placebo. Somnolence described as worse on clozapine.
US PSG. 1999	N=60 clozapine mean dose 2 mg, n=30 placebo, n=30	4 weeks	1 clozapine-treated patient developed leukopenia. 6 deaths occurred during a 12-week open-label extension.
Wolters et al., 1990	N=12 clozapine mean dose 170 mg, n=6 placebo, n=6	~6 weeks	Worsening parkinsonism in 3 clozapine-treated patients.
Olanzapine			
Breier et al., 2002	N=160 olanzapine mean dose 4.2 mg (US, n= 41), 4.1 mg (Europe, n=49) placebo, n=70	4 weeks	Significant worsening of parkinsonism in US patients but not in European sites. Neither mortality nor cerebrovascular adverse events reported.
Nichols et al., 2013	N=23 olanzapine up to 5 mg, n=14 placebo, n=9	4 weeks	Mortality not described and no detailed description of adverse events.
Ondo et al., 2002	N=30 olanzapine mean dose 4.6 mg, n=20 placebo, n=10	9 weeks	6 olanzapine-treated patients compared with 0 placebo-treated patients had worsening of parkinsonism. Mortality and cerebrovascular events not reported.

Abbreviations: US = United States; PSG = Parkinson Study Group
– Not available

These studies have shown that olanzapine and other related drugs may help with PD psychosis, but worsen PD symptoms; while quetiapine has not demonstrated adequate efficacy in the treatment of PD psychosis and lacks long-term safety data (Ballard et al. 2015). Clozapine has demonstrated efficacy in the treatment of PD psychosis, with acceptable risk, but requires burdensome monitoring, which makes it generally impracticable (Seppi et al., 2011). Thus, treating PD psychosis has been extremely challenging as the antipsychotics with dopamine-blocking properties can worsen parkinsonian motor features and have been associated with increased morbidity and mortality in elderly patients with dementia (Goldman and Holden 2014). The lack of effective and well-tolerated available alternative treatments has been cited as a reason for the continued off-label use of atypical antipsychotics to treat PD psychosis patients despite safety issues (Saad et al., 2010).

Consequently, considering the chronic, progressive nature of PD psychosis, and the high incidence and associated disability, distress, and burden, a therapeutic intervention is urgently warranted to effectively manage psychotic symptoms in patients with PD. Importantly, such a treatment should manage the symptoms without exacerbating underlying parkinsonism, accelerating cognitive decline, or increasing the risk for sedation or other adverse events that currently inhibit the use of dopamine-blocking agents. A pharmacologic therapy with these attributes would provide much-needed benefit to these already fragile, elderly patients, as well as their caregivers.

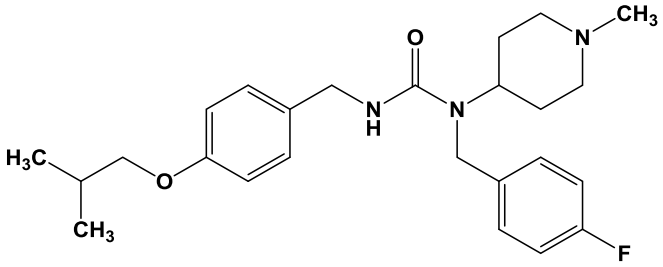
In summary, PD psychosis is a serious progressive medical condition that occurs in over 50% of PD patients over the course of their disease. The onset of psychosis is often a turning point in the disease and, left untreated, can progress quickly to irreversible deterioration. The symptoms of PD psychosis have a significant impact on the course of the patient's disease, their quality of life, and ultimate prognosis. There is no approved treatment for PD psychosis, and the currently available antipsychotics that are used off-label for the treatment of PD psychosis have not demonstrated efficacy in controlled trials, and can cause worsening of PD motor symptoms, have tolerability concerns, or impose extensive monitoring burden. A safe, effective, and approved therapeutic intervention is urgently warranted to effectively manage psychotic symptoms in patients suffering from this debilitating, progressive disorder, and relieve the burden on their caregivers.

4 Pimavanserin Product Description and Regulatory History

4.1 Product Description

Pimavanserin is formulated as a tartrate salt. The chemical name of pimavanserin is urea, *N*-[(4-fluorophenyl)methyl]-*N*-(1-methyl-4-piperidinyl)-*N'*-[[4-(2-methylpropoxy)phenyl]methyl]-,(2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1) (Figure 4-1).

Figure 4–1 Structural Formula for Pimavanserin



The drug product is formulated with standard pharmaceutical excipients as a 17 mg strength, immediate-release tablet for once-daily oral administration. The recommended therapeutic dose of pimavanserin is 34 mg, taken orally as two 17 mg strength tablets once daily with or without food.

4.2 Pimavanserin Regulatory History

The major regulatory and developmental milestones for the pimavanserin program are summarized below.

2003	Development initiated under the IND
2006	Proof of concept Study 006, demonstrated no impairment of motor control and provided preliminary evidence of antipsychotic efficacy
2006	Type C and End-of-Phase 2 meetings with FDA discussed the design of the initial Phase 2b/3 study (Study 012) including doses and duration, the use of the 20-item SAPS-Hallucinations and -Delusions (SAPS-H+D) scale, a subscale of the Scale for the Assessment of Positive Symptoms (SAPS; Appendix A) as the primary psychotic symptom endpoint, and the use of UPDRS as the key secondary endpoint evaluating motor function
2007/2008	Initiation of Phase 2b/3 Studies 012 and 014
2009	Completion of Study 012, which failed to meet primary endpoint, and subsequent decision to stop Study 014 on the basis of these results

2010	Type C meeting with FDA to review Study 012 data and obtain agreement on design of Study 020, including the SAPS-PD scale (a 9-item shortened version of SAPS-H+D scale) as the primary endpoint as well as specific protocol refinements intended to reduce variability and mitigate placebo response based on the learnings from Study 012
	Initiation of Phase 3 Study 020
2012	Completion of Study 020 with consistent and significant positive outcomes for primary and secondary measures of psychotic symptoms, caregiver burden, and sleep scores for pimavanserin 34 mg vs. placebo. Study 020 also confirmed that pimavanserin treatment does not worsen motor symptoms in PD patients.
2013	Type C meeting with FDA to discuss results of Study 020 and agreement reached to file a New Drug Application (NDA) based on positive results from single study (Study 020) with supportive data from previous studies
2014	Pre-NDA meeting with FDA to discuss content and organization of the NDA
	Breakthrough Therapy Designation granted by FDA
2015	NDA submission in September 2015. Priority Review granted.

5 Pimavanserin Pharmacology and Nonclinical Development

An extensive program of nonclinical studies has been conducted with pimavanserin and includes a comprehensive series of pharmacodynamic studies; complete core battery of safety pharmacology studies; single-dose and repeat-dose oral toxicity studies in mice, rats, and monkeys; a full complement of genotoxicity studies; 2-year carcinogenicity studies in rats and mice; assessment of fertility and early embryonic development; and absorption, distribution, metabolism, and elimination (ADME) studies.

5.1 Targeted Pharmacologic Approach to Treatment of Psychotic Symptoms in Parkinson's Disease

In *in vitro* receptor binding and functional assays, pimavanserin preferentially targets 5-HT_{2A} receptors, where it displays high potency as an inverse agonist. The only other receptor targeted by pimavanserin with any notable activity is the 5-HT_{2C} receptor. However, the selectivity of pimavanserin for 5-HT_{2A} receptors is more than 10-fold higher compared to selectivity for 5-HT_{2C} receptors (Vanover et al., 2006). An inverse agonist acts as an "antagonist" and blocks not only ligand-mediated activity through the receptor but also constitutive activity that occurs regardless of whether the receptor is occupied by an agonist. Importantly, pimavanserin lacks activity at the 5-HT_{2B} receptor that has been associated with gastrointestinal function and myocardial development.

Literature supports the rationale for the utility of a 5-HT_{2A} inverse agonist in the treatment of PD psychosis (Meltzer et al., 1995; Weiner et al., 2003). In PD patients, the number of 5-HT_{2A} receptors in the motor cortex is increased and visual hallucinations are associated with excessive 5-HT_{2A} transmission in visual processing areas (Huot et al., 2010; Ballanger et al., 2010).

Table 5–1 compares the receptor selectivity of pimavanserin with both typical and atypical antipsychotics, based on data derived from functional antagonist Receptor Selection and Amplification (R-SAT™) assays (Hacksell et al., 2014). The R-SAT platform is an assay system in which the functional activity of a wide selection of gene products or potential drug targets is evaluated through signal transduction pathways that lead to cellular growth, the signals of which are reported using marker gene technologies. A low inhibition constant (K_i) value in Table 5–1 indicates high affinity for that receptor.

Pimavanserin does not exhibit measurable affinity for dopaminergic, histaminergic, adrenergic, or muscarinic receptors that are individually or collectively associated with significant dose-limiting side effects of antipsychotics (Table 5–1).

Table 5–1 Receptor Selectivity of Pimavanserin Compared with Some Typical and Atypical Antipsychotic Drugs (K_i [nM])

Receptor		Pimavanserin	Typical APD	Atypical APDs			
			Haloperidol	Clozapine	Olanzapine	Quetiapine	Risperidone
Serotonergic	5-HT_{2A}	0.4	50	7	2.5	250	0.2
	5-HT_{2B}	--	--	40	80	1100	12
	5-HT_{2C}	16	--	40	80	--	100
	5-HT_{1A}	--	--	--	--	--	--
Histaminergic	H1	--	--	0.5	4	5	60
Muscarinic	M1	--	--	16	60	250	--
	M2	--	--	--	150	nd	--
	M3	--	--	6	250	200	--
	M4	--	--	--	40	150	--
	M5	--	--	30	60	nd	--
Dopaminergic	D1	--	100	250	100	nd	60
	D2	--	0.1	50	4	30	0.5
	D3	--	0.2	200	25	9	13
Adrenergic	Alpha 1A	--	40	8	100	--	3
	Alpha 1D	nd	--	150	--	--	50
	Alpha 2A	--	--	300	--	--	20
	Alpha 2B	--	--	50	--	--	50
	Alpha 2C	--	50	40	--	--	13

Abbreviations: APD = antipsychotic drug; K_i = inhibition constant; nd = not detected; R-SAT™ = Receptor Selection and Amplification Technology

Data are K_i values in nM derived from functional antagonist R-SAT™ assays, with a low K_i indicating high affinity for that receptor. "—" denotes no response (>1000 nM); "nd" denotes not done.
Source: Hacksell et al., 2014, data on file

D_2-receptor–related risks include extra-pyramidal symptoms and cognitive dulling, and H_1-receptor–mediated side effects include sedative effects that are known to contribute to the risk for fall and infection (Reynolds, 2011; Ballard and Howard, 2006; Kuschel et al., 2015; Spindler et al., 2013). Alpha 1-adrenergic–related side effects, including postural hypotension, and muscarinic-related side effects, including sialorrhea, have been shown to contribute to aspiration risk in patients with PD psychosis (Saenger et al., 2016; Trigoboff et al., 2013; Hinkes et al., 1996).

5.2 Pimavanserin's In Vivo Pharmacodynamic Profile

In addition to showing activity in standard animal models of antipsychotic activity (data on file), pimavanserin has been shown to reverse psychosis-like behaviors in rodent models of PD psychosis and Alzheimer's disease psychosis (McFarland et al., 2011; Price et al., 2012; data on file). In the rodent model of PD psychosis, pimavanserin normalized spontaneous head twitch, augmented amphetamine-induced hyperactivity, and disrupted prepulse inhibition induced by lesions of the *substantia nigra pars compacta*. In all cases, the effects were statistically significant (McFarland et al, 2011; Hubbard et al, 2013; data on file). The

reversal of psychosis-like behaviors was not accompanied by any effect on motor behavior or blockade of dopamine-mediated behaviors. In contrast to clozapine and quetiapine, pimavanserin reduced psychosis-like behavior at dosages more than a 100-fold lower than doses that reduced locomotion, and no dose tested blocked apomorphine-induced rotations, a dopamine-mediated behavior (data on file).

Unlike the sedative properties of current antipsychotics, pimavanserin's 5-HT_{2A} selectivity is expected to impart non-sedative sleep maintenance benefits, consistent with the profile observed for the 5-HT_{2A} antagonists ritanserin, ketanserin, and eplivanserin (Monti, 2010).

5.3 Safety Pharmacology

Safety pharmacology studies were conducted to assess the effects of pimavanserin on the cardiovascular, respiratory, gastrointestinal function, and central nervous systems.

Pimavanserin inhibited human ether-à-go-go related gene (hERG) potassium current with an IC_{50} of 210 nM.

Oral administration of pimavanserin at 1, 10, and 100 mg/kg in telemetered cynomolgus monkeys had no marked effects on arterial blood pressure (systolic, diastolic, and mean) or heart rate, or on electrocardiogram (ECG) parameters. Statistically significant QTc interval prolongation was observed at two time points (2 and 6 hours) in the high-dose group (100 mg/kg); the magnitude of the effect was considered small and not time-related, thus the relationship to pimavanserin treatment was considered uncertain. There were no changes in ECG parameters in the 1-, 3-, or 12-month toxicity studies in monkeys at doses up to 60 mg/kg/day.

The potential for QT prolongation in humans has been tested in a thorough QT study (TQT) and the results of this study are discussed in Section 9.6.1.

5.4 Nonclinical Toxicology Summary

A comprehensive nonclinical toxicology program has been completed, including single-dose oral toxicity studies in rats; repeat-dose oral toxicity studies in mice (up to 13 weeks), rats (up to 6 months), and monkeys (up to 12 months); genotoxicity tests both *in vitro* and *in vivo*; 2-year oral carcinogenicity studies in mice and rats; and a full developmental and reproductive toxicity program.

Across the species, key findings included decreases in body weight or decreases in body weight gain and systemic microscopic alterations consistent with phospholipidosis (often described as cytoplasmic vacuolation or accumulation of vacuolated or foamy macrophages). Vomiting (emesis) was dose-limiting in monkeys.

As predicted from pimavanserin physicochemical properties, findings of intracellular lipid accumulation consistent with phospholipidosis were observed in multiple tissues of rats, mice, and monkeys administered repeated doses of pimavanserin. The phospholipidotic changes associated with pimavanserin treatment in mice (no-observed-effect-level [NOEL] for phospholipidosis of ≥13-fold) and monkeys (NOEL of 4-fold) appeared to be adaptive and reversible. In rats, lungs and kidneys were the tissues most often and most severely affected.

Pleural/subpleural fibrosis of the lung was diagnosed in one rat study of 6-month oral administration (high-dose females dosed for 3 months), in one high-dose and one control rat at 13 or 26 weeks, respectively. This effect was more prominent (8 of 38 pimavanserin-treated rats) at the end of the 6-month recovery period. A panel of two experienced toxicologic pathologists carried out a further review of all lung slides from this study. Trichrome staining to visualize collagen was used for this review. Chronic/subacute inflammation and pleural/subpleural fibrosis were observed and considered secondary to the moderate to severe phospholipidosis in the lung, where the lung was overloaded with foamy macrophages (phospholipidosis) causing increases in lung weight (up to 3-fold control weights) and difficulty breathing. The distribution of the pleural/subpleural fibrosis, including adjacent alveolar interstitium, was determined with Masson's trichrome staining. This pleural/subpleural fibrosis was consistent with irritation of the pleura and perhaps with interference of the lymph drainage by the severe infiltration of phospholipid-laden macrophages. This infiltration, resulting in lung weights up to three times those of controls, added to the physical effect of rubbing of the parietal and visceral pleuras during the process of respiration. These findings were considered histologically different from chronic interstitial lung disease as seen in humans and animals with direct acting lung toxicants. The findings lack the diffuse alveolar cell proliferation, the diffuse initial inflammatory infiltrate and the subsequent diffuse collagen infiltration characteristic of pulmonary fibrosis in humans and of most of the animal models of pulmonary fibrosis reported. The pleural/subpleural fibrosis was observed in an increased severity because the fibrosis became more visible after lungs returned to nearly complete recovery from their enlarged size after the end of the drug-free period. The observed lung pleural/subpleural fibrosis and chronic inflammation occurred at doses that exceeded the maximum tolerated dose and at exposures that were 18- and 10-fold, respectively, the intended human exposure (based on AUC). As these observations were primarily a high-dose effect in a single rat study and histologically different from chronic interstitial fibrosis caused by directly acting lung toxicants, the finding in rats is unlikely to be relevant to clinical use.

In a 14-day combination repeat-dose toxicity study, co-administration of pimavanserin with levodopa and carbidopa had little effect on the pimavanserin safety profile.

No evidence of a mutagenic effect of pimavanserin was observed in a battery of genotoxicity studies. Pimavanserin showed no evidence of carcinogenic potential in 2-year studies conducted in rat and mouse.

In a fertility study in rats, there were no treatment-related effects on mating, fertility, or pregnancy indices. Treatment-related changes observed in uterine parameters were suggestive of maternal reproductive toxicity and/or embryotoxicity (at the high-dose level). Dose-related changes in sperm parameters and microscopic changes in the epididymis (vacuolation) occurred in males.

There were no indications that pimavanserin affects embryo-fetal development in rats or rabbits.

In a peri- and postnatal development study in the rat, effects on pup viability and pup weights were seen at maternally toxic doses. There were no pimavanserin-related effects on sexual maturation, neurobehavioral, or reproductive function in the F1 generation rats.

5.5 Pimavanserin ADME Properties

Pimavanserin is extensively metabolized, predominantly in the liver. Pimavanserin undergoes multiple sequential metabolic steps to form hydrophilic metabolites that can be efficiently eliminated in urine or bile. There were no unique metabolites identified in human subjects compared with monkeys, rabbits, rats, and mice, the species used for non-clinical safety testing.

The major metabolite formed *in vitro* by human liver microsomes, AC-279 (*N*-desmethyl-pimavanserin), was identified as a significant circulating metabolite in humans *in vivo*. AC-279 has similar receptor activity to pimavanserin and is covered by available toxicity data. The elimination half-life of AC-279 is ~65 hours.

In vitro studies established that the primary metabolites of pimavanserin are formed predominantly by the cytochrome P450 (CYP) 3A4 enzymes with a minor role for CYP2J2, an enzyme whose substrates are also substrates of CYP3A4, along with small contributions from numerous other CYP and flavin monooxygenase enzymes. Transporters play no significant role in the disposition of pimavanserin, consistent with its rapid dissolution, high aqueous solubility, and extensive tissue distribution. Only about 2% of pimavanserin is eliminated as unchanged drug in urine (0.55%) and feces (1.53%).

6 Pimavanserin Clinical Pharmacology

Pharmacokinetic (PK) evaluation of pimavanserin has been evaluated, consistent with current regulatory guidance.

6.1 Pharmacokinetic Properties

Pimavanserin is highly permeable and highly soluble in the physiological pH range. It demonstrates linear (dose-proportional) PK after administration of single doses, ranging from 17 to 255 mg, and multiple doses, ranging from 43 to 128 mg, to healthy subjects (Appendix B, Table 3). The C_{max} and AUC increased in proportion to the dose, and oral clearance (CL/F) was comparable across the ranges of single and multiple doses.

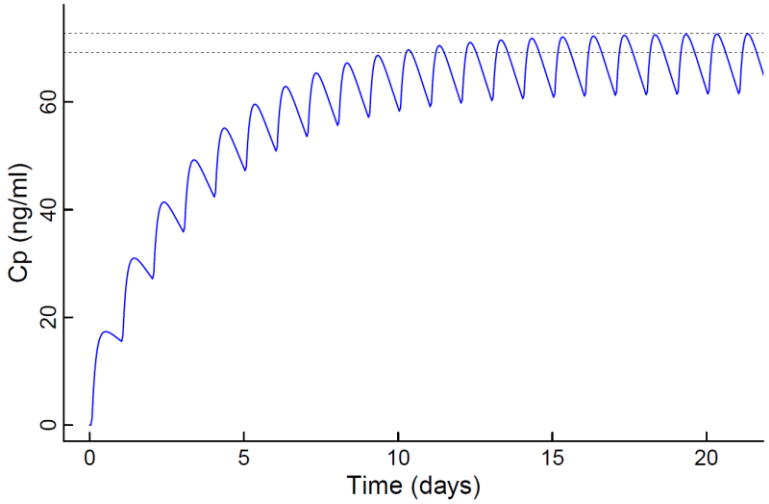
Based on population PK analysis, the PK of pimavanserin is similar in PD subjects and healthy volunteers. No dosage adjustments are anticipated to be necessary on the basis of age, gender, ethnicity, or body mass.

The *in vitro* binding of pimavanserin to human plasma protein was 95%, consistent with the *in vivo* protein binding of 91% to 97%.

The C_{max} of pimavanserin following single dosing is reached at a median time to maximum plasma concentration (T_{max}) of 6-9 hours after dosing under fasted conditions. When administered with a high-calorie/high-fat meal, there is no increase in either C_{max} or AUC; the median T_{max} increases to 11 hours.

The apparent plasma elimination half-life ($t_{½}$) of pimavanserin is about 57 hours and steady state is achieved in 12 days (5 half-lives) of once-daily dosing (Figure 6–1). Consistent with the $t_{½}$ and 24-hour dosing interval, steady-state C_{max} were 3.8- and 4.2-fold greater and AUC_{0-24} values were 4.2- and 4.4-fold greater than single-dose values after daily dosing for 20 days with 17 and 68 mg pimavanserin, respectively (Study 018).

Figure 6–1 Simulation of a Typical Concentration Profile of Pimavanserin Following Daily Dosing with 34 mg Pimavanserin



The "typical", pimavanserin plasma concentration (obtained from the population pharmacokinetic model in Phase 3) is displayed. Dotted lines appear at 95% and 100% of the steady-state C_{max}.

6.2 Drug-Drug Interactions

The potential for pimavanserin to be involved in pharmacokinetic drug-drug interactions in humans was assessed in standard *in vitro* metabolism and transporter studies.

Cytochrome P450-Based Interactions

On the basis of *in vitro* data that suggested the potential for inhibition of pimavanserin's metabolism by a strong inhibitor of CYP3A4, a clinical study (023) was conducted to evaluate the effects of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of pimavanserin. On Day 1, subjects received a single oral dose of pimavanserin 34 mg (2 × 17 mg tablets) under fasting conditions. On Day 15, subjects began taking ketoconazole 400 mg (2 × 200 mg tablets) orally once daily for 14 days. A single oral dose of pimavanserin 40 mg was administered under fasting conditions 60 minutes after the fifth ketoconazole dose (on Day 19). Blood samples were collected for 336 h to determine the PK of pimavanserin and selected metabolites. Treatment with ketoconazole increased the plasma C_{max} of pimavanserin 1.5-fold and increased $AUC_{0\text{-}336h}$ 3-fold. These results are consistent with *in vitro* data demonstrating a major role for CYP3A4 in pimavanserin metabolism. The plasma elimination $t_{½}$ of pimavanserin increased from 58.2 hours to 89.2 hours. Pimavanserin is dosed once-daily and thus accumulates with daily administration; the increased $t_{½}$ would result in additional accumulation if coadministered with a strong CYP3A4 inhibitor. Pharmacokinetic simulations were therefore performed to predict the impact of strong inhibition of CYP3A4 on the steady-state C_{max} of pimavanserin. These simulations

demonstrated that pimavanserin C_{max} after a 34 mg once-daily dose would increase 2.9-fold, from 73 to 209 ng/mL. If administration of a strong CYP3A4 inhibitor were countered with a simultaneous 50% reduction in dose (from 34 mg/day to 17 mg/day), C_{max} would increase ~1.4-fold, from 73 ng/mL to 104 ng/mL. Therefore, a 50% dose reduction is recommended when pimavanserin is coadministered with moderate to strong inhibitors of CYP3A4.

On the basis of *in vitro* data that indicated pimavanserin is a reversible inhibitor of CYP3A4 and AC-279 is an inducer of CYP3A4, the pharmacokinetics of midazolam, a sensitive *in vivo* probe drug for CYP3A4, were evaluated in the presence of pimavanserin in humans (Study 029). The results showed that pimavanserin has no immediate or delayed effect on midazolam exposure (no induction or inhibition of CYP3A4) following dosing with 34 mg pimavanserin for up to 38 days. No dose adjustment is therefore required for other CYP3A4 substrates when coadministered with pimavanserin.

Although not evaluated in an *in vivo* clinical drug-drug interaction study, the concomitant use of a potent CYP3A4 inducer (e.g., phenytoin, carbamazepine, rifampin, avasimibe, and St. John's wort) is likely to increase pimavanserin clearance and thereby reduce plasma C_{max} and AUC. Proposed labeling states that if concomitant use of a CYP3A4 inducer cannot be avoided, the possibility to observe some reduction in antipsychotic efficacy cannot be excluded.

Coadministration of Sinemet® (immediate-release carbidopa/levodopa) and pimavanserin (Study 024) resulted in no significant effect on levodopa exposure. This supports the conclusion that concomitant use of pimavanserin with Sinemet in PD psychosis patients will not result in worsening of motor symptoms. This conclusion is further substantiated by clinical results observed in PD psychosis subjects in which nearly all subjects received some form of antiparkinson's medication and in which the mean effect of pimavanserin on Unified Parkinson's Disease Rating Scale Parts II and III (UPDRS Parts II+III) scores was no different from scores with placebo.

7 Overview of Clinical Development Program

A tabular summary of the complete clinical program for pimavanserin is provided in Appendix B, Table 1.

The clinical efficacy and safety of pimavanserin have been evaluated in a total of 21 completed studies and 4 ongoing studies. Overall, as of 06 January 2016, an estimated 1237 subjects have been exposed to pimavanserin, comprising 645 subjects with PD/PD psychosis (of which 616 had PD psychosis), 177 subjects diagnosed with schizophrenia, 346 healthy subjects, and approximately 69 subjects with Alzheimer's disease psychosis in the ongoing placebo-controlled study. Total subject exposure in PD psychosis exceeds 900 person-years. The longest single exposure is in a subject with over 10 years of continuous treatment with pimavanserin.

Early safety and tolerability studies in healthy subjects established a maximum tolerated dose of 85 mg, with nausea and vomiting being reported as the dose-limiting adverse events following multiple dosing. Pharmacokinetic studies conducted in pimavanserin-treated PD subjects indicated that the safety and pharmacokinetic profiles were similar to those seen in healthy subjects and supported proceeding with subsequent PD psychosis trials.

The safety and efficacy of pimavanserin in subjects experiencing PD psychosis were evaluated in four short-term placebo-controlled studies and two long-term open-label studies. In these studies, a range of pimavanserin doses was evaluated (8.5 to 51 mg) with a 34 mg once-daily dose being selected and evaluated as the recommended clinical dose. In these studies (except Studies 006 and 010, in which subjects underwent dose escalation at periodic intervals), subjects received a fixed daily dose of pimavanserin.

With respect to the patient population studied, the entry criteria across all PD psychosis studies remained consistent with the NINDS/NIMH established diagnostic criteria for PD psychosis, as published by a Movement Disorder Society task force in 2007. Across pivotal Study 020 and the studies that provided supportive data (006, 012, and 014), as well as long-term extension studies (010 and 015) subjects were required to meet the following requirements:

- a diagnosis of PD established at least 1 year prior to study entry
- psychotic symptoms (hallucinations and/or delusions) that started after the PD diagnosis, that were present for at least 1 month, and that were sufficiently severe and frequent to warrant treatment with an antipsychotic drug
- a Mini-Mental State Examination (MMSE) score ≥21 and sufficient cognitive function to be able to self-report symptoms

Primary evidence of efficacy of pimavanserin in the treatment of PD psychosis derives from the results of Study 020, a 6-week, double-blind, placebo-controlled, outpatient study of pimavanserin 34 mg once daily.

In addition to the positive efficacy data from pivotal Study 020, the efficacy of pimavanserin in PD psychosis is supported by data from the three controlled clinical studies (Studies 006, 012, and 014) conducted prior to Study 020. These studies played an important role in the iterative development of the optimal study design and efficacy assessment tools for evaluation of PD psychosis treatment and provide supportive efficacy data.

The chronology, major design features, and results of the four short-term, placebo-controlled clinical studies of pimavanserin in PD psychosis subjects are described below and outlined in Appendix B, Table 2. A tabular summary of the complete clinical program for pimavanserin is provided in Appendix B, Table 1.

The first controlled study, a Phase 2 proof-of-concept study (006), demonstrated that doses up to 51 mg of pimavanserin were well tolerated and, as assessed by UPDRS Parts II+III, did not worsen motor control in PD psychosis subjects. Additionally, greater improvements in psychosis were observed in pimavanserin-treated subjects than placebo-treated subjects. Data from this study supported further development of pimavanserin as a treatment for PD psychosis.

Based on the results of Study 006, two placebo-controlled Phase 2b/3 studies with pimavanserin were initiated. Both studies employed a similar design: 6-week, placebo-controlled, two active-arm studies. One Phase 2b/3 study (Study 012) tested 8.5 and 34 mg doses of pimavanserin and the second study (Study 014) tested 8.5 and 17 mg doses.

The first of the Phase 2b/3 studies (012) did not achieve the specified primary endpoint, with no statistical separation from placebo in the reduction of psychotic symptoms observed for either of the pimavanserin doses tested. While the 8.5 mg pimavanserin dose showed no indication of antipsychotic effect, signals of efficacy were seen for the 34 mg dose in a subset of subjects. Since Study 014 was designed identically to Study 012, except for the lower dose range, the decision was made to discontinue the study early, with about half of the intended patient enrollment.

Learning points from Studies 006, 012, and 014 led to a new Phase 3 study, pivotal Study 020. Study 020 was designed using optimized methodology for assessing psychotic symptoms in PD subjects. The shortened, 9-item SAPS-PD scale (derived from the 20-item SAPS-H+D scale; Appendix D) was implemented as the primary measure of efficacy. Additionally, design features to minimize variability and placebo response were included in the study protocol.

In Study 020, pimavanserin demonstrated statistically significant and clinically meaningful superiority over placebo in antipsychotic efficacy on the primary and secondary efficacy endpoints. Importantly, positive treatment effect did not come at the expense of motor control. Additionally, improvements in caregiver burden and sleep-related measures were observed in the pimavanserin treatment group.

The weight of evidence across Study 020 and supportive data from controlled Studies 006, 012, and 014, as well as consistency of observations across different efficacy measures, assessors/reporters, assessment methodologies and various sensitivity efficacy analyses support the conclusion that pimavanserin is an effective treatment for patients experiencing PD psychosis.

In addition to short-term, placebo-controlled studies, two open-label extension studies, 010 and 015, assessed long-term safety in PD psychosis subjects. The first of these was Study 010 that enrolled 39 subjects who completed Phase 2 Study 006. As in Study 006, flexible doses of 17, 34, and 51 mg were allowed. Study 015, which remains ongoing (see below), enrolled 459 subjects from the Phase 2b/3 and Phase 3 placebo controlled trials, Studies 012, 014, and 020. The majority of subjects who completed the short-term placebo-controlled studies elected to enter the long-term extension studies. In Study 015, all subjects were given 34 mg doses throughout the study.

Detailed results of the above short-term controlled and long-term safety studies are presented in the sections that follow.

As of the safety cutoff date (06 January 2016), the following clinical studies of pimavanserin are ongoing:

- a Phase 3, long-term, open-label extension study (015) in subjects with PD psychosis
- a Phase 2 placebo-controlled study (019) in subjects with Alzheimer's disease psychosis
- studies to evaluate the effects of hepatic (025) and renal impairment (026) on the pharmacokinetics and tolerability of pimavanserin

8 Efficacy Studies and Results

The efficacy of pimavanserin 34 mg for the treatment of PD psychosis was established in a Phase 3, pivotal outpatient Study 020, in which pimavanserin 34 mg was administered once daily, for up to 6 weeks and compared with placebo (Section 8.3.2).

In addition to the positive efficacy data from pivotal Study 020 (Section 8.3.2), supportive findings of efficacy of pimavanserin in PD psychosis are provided by three other placebo-controlled studies that were either 4 weeks (006) or 6 weeks in duration (012 and 014) (Section 8.1).

Open-label, uncontrolled efficacy outcomes are summarized from two long-term, open-label extension studies (010 and 015) (Section 8.4).

Table 8–1 shows the timelines for the three 6-week placebo-controlled PD psychosis studies and the open-label extension studies into which subjects could enroll.

Table 8–1 Pimavanserin Phase 2b/3 Studies

Study Type	Study #	Subjects, N	Duration Primary Endpoint	Dose(s)
Concept Phase 2	006	60	4 weeks UPDRS Parts II+III	PBO, 17, 34, 51 mg flexible titration
Phase 2b/3	012 014	298 123	6 weeks SAPS-H+D	PBO, 8.5, 34 mg PBO, 8.5, 17 mg
Pivotal Phase 3	020	199	6 weeks SAPS-PD	PBO, 34 mg
Open-label Extension Studies	010 015	498	Ongoing 10+ years Safety Assessments	PBO, 17, 34, 51 mg flexible titration 34 mg

8.1 Controlled Phase 2 and Phase 2b/3 Studies

8.1.1 Phase 2 Study 006

Study 006 was a Phase 2, proof-of-concept study. It enrolled 60 subjects with PD psychosis in a flexible, dose escalating, 4-week, placebo-controlled design. Pimavanserin doses were escalated from 17 to 34 to 51 mg at weekly intervals as per the Investigator's discretion based on observed clinical effects. Single step dose reductions were allowed during that period for adverse events (AEs) or intolerance. The primary endpoint in this trial was assessment of motor function, as measured by the change from Screening/Baseline (up to 14 days prior to the first dose on Day 1) to Week 4 in the UPDRS Parts II+III total score. At Week 4, there

was no difference between treatment arms with respect to change in UPDRS Parts II+III total score. Both pimavanserin and placebo showed a small improvement in this endpoint with a minimal and non-significant treatment difference of 2.88 points (least squares [LS] mean change from baseline -2.47 for pimavanserin, -5.35 for placebo; 95% confidence interval [CI] -1.78 to 7.55; p=0.220; modified intent-to-treat [mITT] last observation carried forward [LOCF]).

Antipsychotic efficacy was assessed as a secondary outcome using the SAPS-H+D measure as well as CGI-S. The full Scale for the Assessment of Positive Symptoms (SAPS; [Andreasen, 1984 {Appendix A}]) was originally developed for schizophrenia but was adapted for use in early PD psychosis studies by using the combined score of the 13-item hallucinations (H) and 7-item delusions (D) domains (SAPS-H+D). In general, psychosis scores improved in both pimavanserin and placebo subjects from baseline to Week 4 (treatment difference 3.7 points for the SAPS-H+D [LS mean change from baseline -4.9 for pimavanserin, -1.2 for placebo; 95% CI: -8.5 to 0.8; p=0.106]; treatment difference 0.2 points for CGI-S [LS mean change from baseline -0.4 for pimavanserin and -0.1 for placebo; 95% CI: -0.9 to 0.4; p=0.448]). The mean final daily dose in the active group of Study 006 was 38.1 mg compared with the equivalent of 45.0 mg in the placebo group.

In summary, this small Phase 2 study demonstrated that pimavanserin does not adversely affect motor function in PD subjects and provided signals of antipsychotic efficacy of pimavanserin in subjects with PD psychosis.

8.1.2 Phase 2b/3 Study 012

Study 012 was a double-blind, randomized, placebo-controlled, outpatient study that evaluated the safety and efficacy of pimavanserin 34 mg and 8.5 mg compared with placebo in 298 subjects with PD psychosis for up to 42 days (6 weeks). The study was conducted in three regions: US, Europe, and India. Study 012 included 3 weeks of screening, 6 weeks of treatment, and 4 weeks of follow-up. There was no placebo run-in period and subjects did not receive study drug during the screening period. Eligible subjects were required to have screening MMSE scores ≥21, Neuropsychiatric Inventory hallucinations and delusions subscales (NPI-H+D) scores ≥4, and baseline SAPS-H+D scores ≥5. Nearly all subjects (99%) in Study 012 were on PD medications at entry. PD medications were required to be stable from 30 days prior to study start. No concomitant antipsychotic medications were allowed. Both the subject and caregiver provided consent for study participation. Post-baseline study visits during the treatment phase were at Weeks 1, 2, 4, and 6. Subjects who completed 6 weeks of treatment and who might benefit from pimavanserin treatment were eligible to enter the open-label extension Study 015. For subjects who terminated early or

did not enter Study 015 at the Week 6 visit (end of treatment), a follow-up (Day 70 [Week 10]) safety visit was conducted.

The primary objective of Study 012 was to evaluate the antipsychotic efficacy of pimavanserin in subjects with PD psychosis, as measured by a decrease in the severity and/or frequency of hallucinations and/or delusions. The primary efficacy variable in Study 012 was the mean change from baseline to Week 6 on the 20-item SAPS-H+D scale using the LOCF method for the mITT analysis set (N=287)[1]. At US study centers, SAPS-H+D assessments were conducted via live video interviews by central raters blinded to study design, entrance criteria, visit number, treatment assignment, and any study data for the subject or caregiver. At non-US study centers (i.e., those in Europe and India), site-based raters were trained and certified to administer SAPS assessments in their respective languages.

Demographics and selected baseline characteristics for all randomized analysis set are presented in Table 8–2 and Table 8–3.

Table 8–2 Subject Demographics (Study 012; All randomized, N=298)

Demographics	Pimavanserin		Placebo (N=98)
	8.5 mg QD (N=101)	34 mg QD (N=99)	
Age (years)			
Mean (SD)	69.2 (8.59)	69.2 (7.99)	69.6 (9.65)
Median (min, max)	69.0 (44, 87)	70.0 (40, 84)	72.0 (43, 86)
Age Group, n (%)			
<65 years	30 (29.7%)	24 (24.2%)	27 (27.6%)
65-75 years	49 (48.5%)	52 (52.5%)	41 (41.8%)
>75 years	22 (21.8%)	23 (23.2%)	30 (30.6%)
Sex, n (%)			
Male	64 (63.4%)	75 (75.8%)	51 (52.0%)
Female	37 (36.6%)	24 (24.2%)	47 (48.0%)
Race Group, n (%)			
White	87 (86.1%)	86 (86.9)	83 (84.7%)
Non-white	14 (13.9%)	13 (13.1%)	15 (15.3%)

[1] In Study 012, of 298 randomized subjects, 11 subjects did not have a post-baseline SAPS-H+D value and therefore were not included in the mITT analysis set (N=287). See Appendix B, Figure 1.

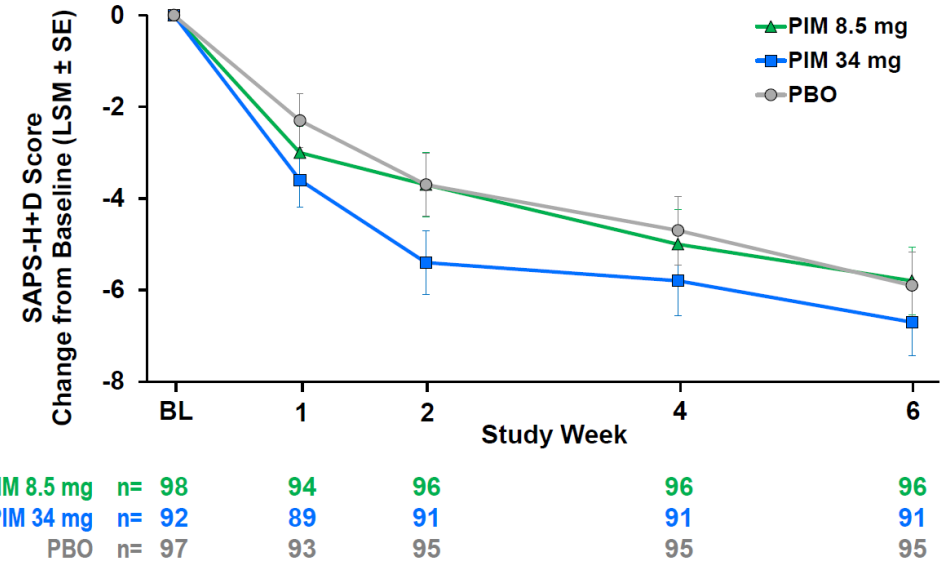
Table 8–3 Selected Baseline Characteristics (Study 012; All Randomized, N=298; Mean [SEM])

Characteristic	Pimavanserin 8.5 mg QD (N=101)	Pimavanserin 34 mg QD (N=99)	Placebo (N=98)
SAPS-H+D score	16.9 (0.98)	15.3 (0.82)	13.9 (0.80)
SAPS-H score	10.0 (0.57)	10.2 (0.54)	8.4 (0.48)
SAPS-D score	6.9 (0.62)	5.0 (0.51)	5.4 (0.56)
NPI-H+D score (Screening)	9.8 (0.52)	9.9 (0.46)	8.6 (0.42)
MMSE score (Screening)	26.2 (0.28)	26.1 (0.27)	26.4 (0.25)
CGI-Severity score	3.9 (0.10)	3.8 (0.10)	3.8 (0.10)
UPDRS Parts II+III score	51.92 (2.12)	52.33 (2.20)	55.28 (2.09)
Duration of PD (months)	97.5 (6.38)	86.2 (6.04)	116.1 (8.26)
Duration of PD psychosis (months)	19.5 (2.05)	21.2 (2.57)	23.2 (3.66)

Abbreviations: SEM=standard error of the mean

Study 012 did not achieve the prespecified primary objective. In the primary analysis (mITT), all treatment arms showed marked improvements in LS mean SAPS-H+D scores: 5.9 points for placebo, 5.8 points for 8.5 mg pimavanserin, and 6.7 points for 34 mg pimavanserin. Hence, neither pimavanserin treatment group showed a statistically significant separation from placebo at Week 6 (Figure 8–1).

Figure 8–1 SAPS-H+D Change from Baseline (Study 012; mITT, LOCF, N=287)



In a protocol prespecified subgroup analysis by region, however, it was observed that for the US sites (which also coincides with the sub-set of sites where central independent rating of the primary efficacy measure [SAPS-H+D] was used) the pimavanserin 34 mg dose showed a trend ($p<0.1$) toward improvement compared to placebo (treatment difference 2.5 points; LS

mean change from baseline -6.9 for pimavanserin 34 mg, -4.4 for placebo; 95% CI: -5.4 to 0.5; p=0.099) (Figure 8–2; Figure 8–3). At sites where SAPS-H+D was assessed by a site-based rater (i.e., non-US sites), there was no statistical difference between treatment arms (Figure 8–2).

Figure 8–2 SAPS-H+D Change from Baseline at Week 6, All Regions (Study 012; mITT, LOCF, N=287)

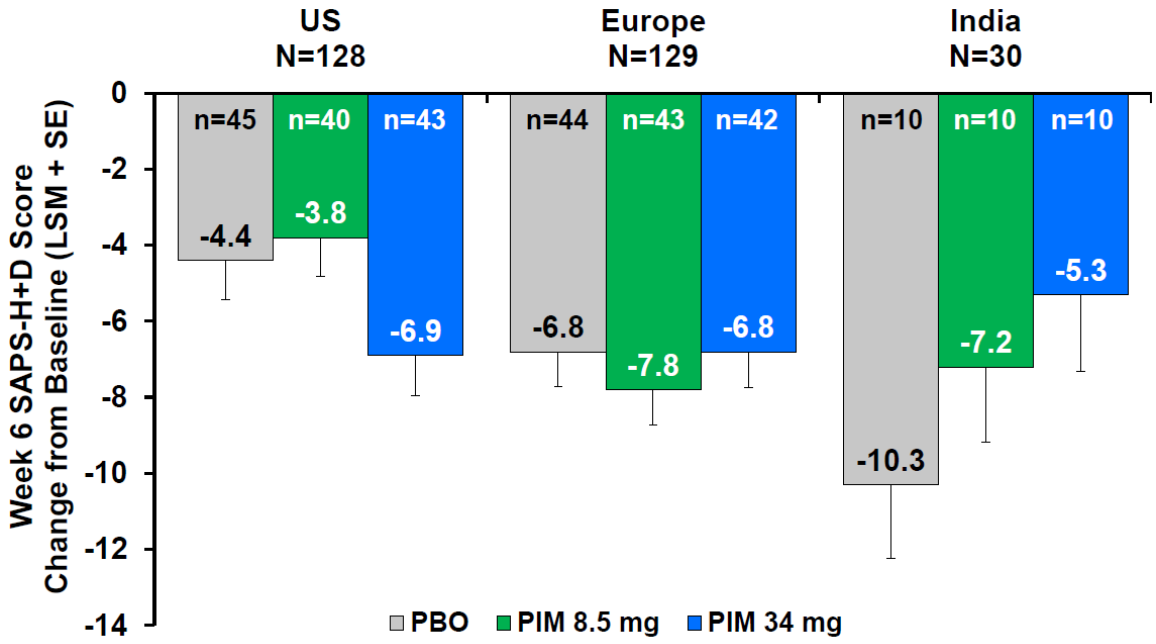
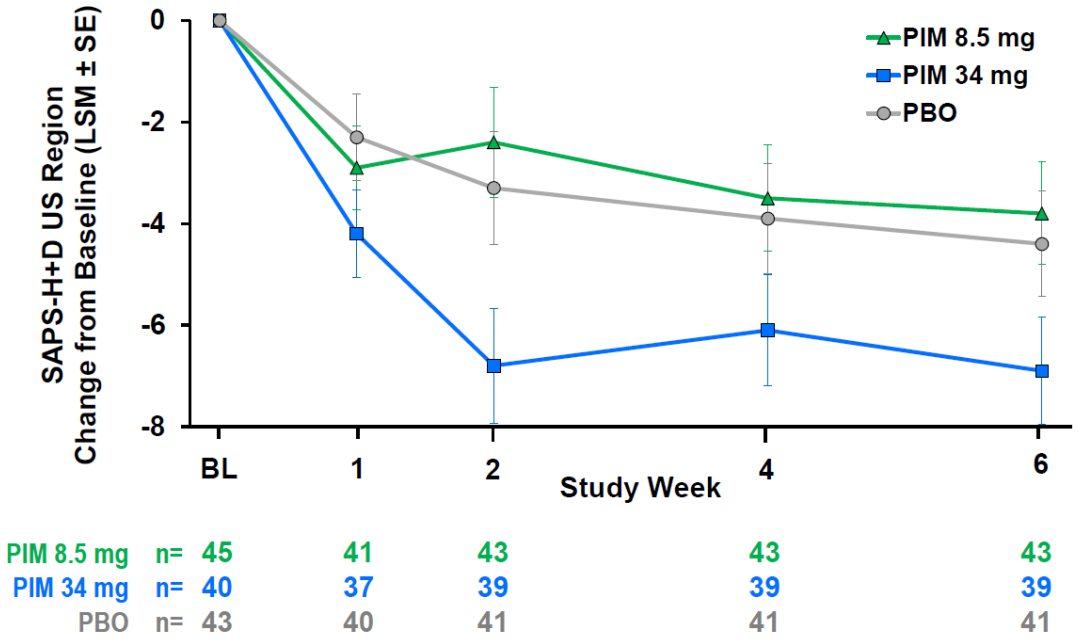
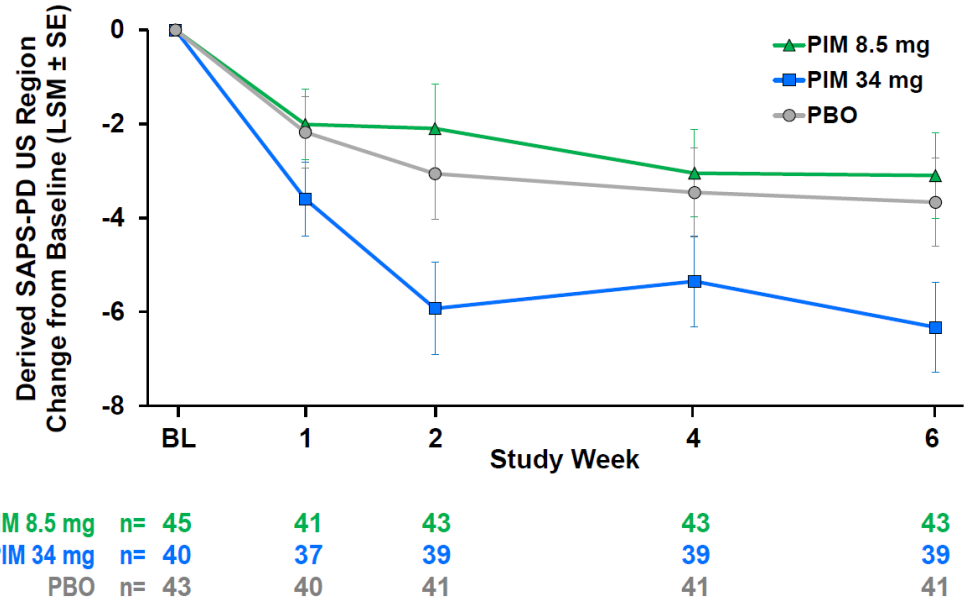


Figure 8–3 SAPS-H+D Change from Baseline, US Region (Study 012; mITT, LOCF, N=128)



In a post-hoc analysis of the primary endpoint, the 20-item SAPS-H+D data were analyzed using the SAPS-PD scale (the 9-item subset as used in Study 020). For a description of the development of the SAPS-PD scale from the SAPS-H+D scale see Section 8.3.1.1.1. Using this approach, the reported difference between the pimavanserin 34 mg group and placebo in the US region was in favor of pimavanserin (treatment difference was 2.66 points [95% CI: -5.31 to -0.00]; p=0.0498 [see Figure 8–4]). For sites outside of the US, there was no difference in SAPS-PD scores between treatment arms.

Figure 8–4 Derived SAPS-PD Change from Baseline, US Region (Study 012; mITT, LOCF, N=128)



The results of Study 012 also showed that pimavanserin did not negatively affect motor function in PD psychosis subjects (UPDRS Parts II+III treatment difference -0.33 [95% CI: -3.08 to 2.43] for pimavanserin 34 mg vs. placebo, with an LS mean change from baseline of -2.83 for pimavanserin 34 mg and -2.50 for placebo; treatment difference of 0.98 [95% CI: -1.74 to 3.70] for pimavanserin 8.5 mg vs. placebo, with an LS mean change from baseline of -1.52 for pimavanserin 8.5 mg). As indicated above, both treatment groups showed slight improvement in their motor symptoms.

Consistent with the overall primary analysis, no significant separation between treatments was observed on the secondary endpoints of CGI-S and CGI-I. The treatment difference in CGI-S score was -0.1 (95% CI: -0.4 to 0.3), with an LS mean change from baseline of -0.8 for pimavanserin 34 mg and -0.8 for placebo; p=0.756; the treatment difference was 0.2 (95% CI: -0.1 to 0.5) for pimavanserin 8.5 mg vs. placebo, with an LS mean change from baseline of -0.6 for pimavanserin 8.5 mg; p=0.274). The LS mean CGI-I score for placebo was 3.08 for placebo, 3.12 for pimavanserin 8.5 mg, and 2.85 for pimavanserin 34 mg), and the magnitude of the treatment difference (pimavanserin minus placebo) was -0.2 (95% CI: -0.6 to 0.2; p=0.254) in the 34 mg group and 0.0 (95% CI, -0.6 to 0.4; p=0.807) in the 8.5 mg group. Analysis by region also did not reveal any differences in the response pattern on CGI.

In summary, Study 012 did not meet its primary endpoint. However, there were some important lessons learned from the results of this study:

- Methodological issues notwithstanding, it appeared that the 34 mg dose of pimavanserin did show an efficacy signal in the US.
- Pimavanserin did not worsen motor function in PD psychosis subjects.
- Independent rating of psychotic symptoms may be critical for reducing "noise" and increasing reliability of primary efficacy assessment.

8.1.3 Phase 2b/3 Study 014

On the basis of the results from Study 012, ACADIA elected to stop Study 014 early. Study 014 had the same study design and methodology as Study 012, was also conducted internationally, and had the same entry criteria. Compared to Study 012, Study 014 tested lower doses of pimavanserin (8.5 mg and 17 mg). The planned sample size for Study 014 was 279 subjects. A total of 123 subjects were enrolled before study termination: 54 at US sites and 69 at non-US sites (all in Europe). The mITT analysis set included 117[2] subjects.

Demographics and selected baseline characteristics for the all randomized analysis set are presented in Table 8–4 and Table 8–5. Nearly all subjects (93%) were on PD medications at study entry.

Table 8–4 Subject Demographics (Study 014; All Randomized, N=123)

Demographics	Pimavanserin		Placebo (N=40)
	8.5 mg QD (N=40)	17 mg QD (N=42)	
Age (years)			
Mean (SD)	71.0 (7.43)	72.1 (8.15)	73.2 (7.87)
Median (min, max)	71.5 (53,90)	73.0 (53, 88)	74.0 (58,88)
Age Group, n (%)			
<65 years	7 (16.7%)	7 (17.1%)	7 (17.5%)
65-75 years	23 (54.8%)	16 (39.0%)	14 (35.0%)
>75 years	12 (28.6%)	18 (43.9%)	19 (47.5%)
Sex, n (%)			
Male	26 (61.9%)	24 (58.5%)	28 (70.0%)
Female	16 (38.1%)	17 (41.5%)	12 (30.0%)
Race Group, n (%)			
White	40 (95.2%)	41 (100.0%)	38 (95.0%)
Non-white	2 (4.8%)	0 (0.0%)	2 (5.0%)

[2] In Study 014, of 123 randomized subjects, 6 subjects did not have a post-baseline SAPS-H+D value and therefore were not included in the mITT analysis set (N=117). See Appendix B, Figure 1.

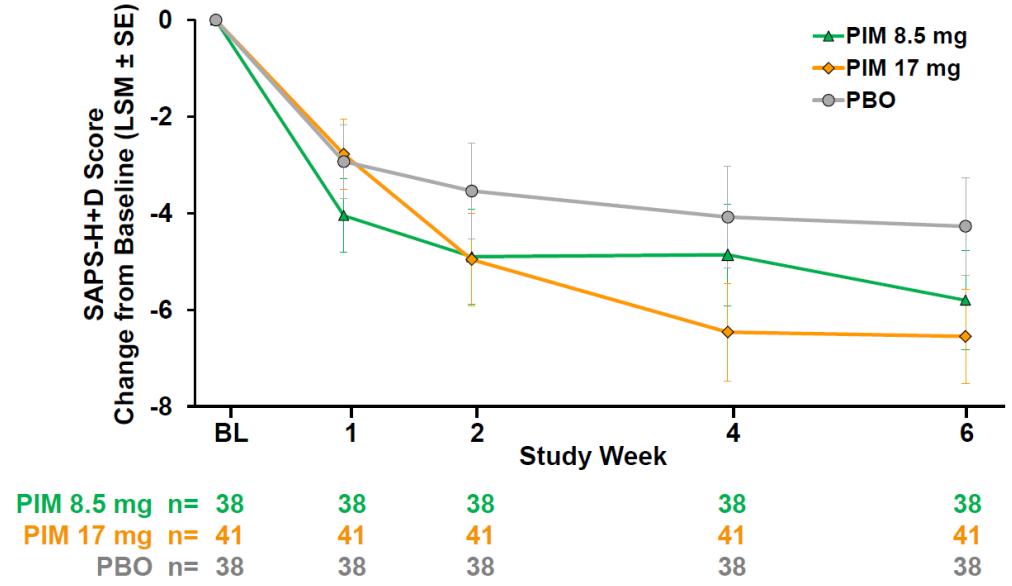
Table 8–5 Selected Baseline Characteristics (Study 014; All Randomized, N=123, Mean [SEM])

Characteristic	Pimavanserin		Placebo (N=40)
	8.5 mg QD (N=42)	17 mg QD (N=41)	
SAPS-H+D score	15.4 (1.62)	15.5 (1.03)	16.6 (1.43)
SAPS-H score	8.9 (0.99)	10.0 (0.69)	10.5 (0.82)
SAPS-D score	6.5 (1.02)	5.5 (0.66)	6.2 (0.98)
NPI-H+D score (Screening)	11.2 (0.90)	10.1 (0.83)	9.9 (0.87)
MMSE score (Screening)	26.6 (0.35)	26.0 (0.45)	26.5 (0.46)
CGI-Severity score	3.8 (0.18)	4.0 (0.16)	4.0 (0.14)
UPDRS Parts II+III score	46.71 (3.10)	47.06 (2.85)	45.08 (3.11)
Duration of PD (months)	113.2 (10.81)	107.8 (10.49)	113.4 (10.10)
Duration of PD psychosis (months)	31.3 (4.35)	24.6 (4.21)	26.9 (4.39)

Abbreviations: SEM=standard error of the mean

Although there were some suggestions of positive efficacy signals with the 17 mg dose, very little can be concluded from the completed analysis due to the premature termination of the study and the small size of the dataset. The primary endpoint based on the SAPS-H+D showed a favorable trend for the 17 mg dose but failed to achieve significance (treatment difference -2.1 [95% CI: -4.9 to 0.8]; LS mean change from baseline -6.5 for pimavanserin 17 mg, -4.4 for placebo; p=0.159) (Figure 8–5).

Figure 8–5 SAPS-H+D Change from Baseline (Study 014; mITT, LOCF N=117)



The results also showed that pimavanserin did not negatively affect motor function in PD psychosis subjects (UPDRS Parts II+III treatment difference -2.04 [95% CI: -5.82 to 1.73] for pimavanserin 17 mg vs. placebo, with an LS mean change from baseline -3.9 for

pimavanserin 17 mg, -1.8 for placebo; treatment difference of -0.05 [95% CI: -3.90 to 3.80] for pimavanserin 8.5 mg vs. placebo, with an LS mean change from baseline -1.9 for pimavanserin 8.5 mg).

Notably, an improvement over placebo was observed for the 17 mg pimavanserin arm on the secondary CGI-I measure (treatment difference of -0.66; 95% CI: -1.21 to -0.11; p=0.020, mITT LOCF analysis of variance [ANOVA]). No statistical separation for pimavanserin 8.5 mg (treatment difference of -0.01; 95% CI: -0.56 to 0.57; p=0.986) was observed. There was a trend toward separation for CGI-S for the 17 mg pimavanserin arm but not the pimavanserin 8.5 mg arm (treatment difference -0.49 [95% CI: -0.98 to 0.01] for pimavanserin 17 mg vs. placebo, with an LS mean change from baseline -0.99 for pimavanserin 17 mg, -0.50 for placebo, p=0.053; treatment difference -0.03 [95% CI: -0.53 to 0.47, p=0.911] for pimavanserin 8.5 mg vs. placebo, with an LS mean change from baseline -0.53 for pimavanserin 8.5 mg).

Considering that Study 014 was stopped with only 123 subjects enrolled (of 287 planned) no meaningful regional subset analysis was possible due to small numbers of observations in each region by dose. Descriptively, however, there was no appreciable difference in response pattern observed between the regions.

In summary, although truncated, Study 014 did corroborate the positive signal seen in Study 012 and confirmed the absence of negative impact on motor function. The signal seen at the 17 mg pimavanserin dose, however, was seen on the secondary efficacy measure only after failure to observe such separation on the primary endpoint.

8.2 Key Learnings from Phase 2b/3 Studies Taken into Further Development

A number of key findings from Study 012 led to the modifications of the methodology for Study 020. Specific protocol refinements intended to optimize study design, reduce variability and placebo response included (see Appendix B, Table 2):

- Study 020 required enrollment of subjects with moderate-to-severe symptoms that were sufficiently frequent (i.e., occurring weekly) to be accurately measured over a 6-week treatment period. Eligible subjects were required to have screening NPI-H scores ≥4 or NPI-D ≥4, or NPI H+D ≥6; and baseline SAPS-H or SAPS-D global item (H7 or D13) score ≥3, and a score ≥3 on at least one other nonglobal item using the 9-item SAPS-PD. The NPI and SAPS scores required for Study 020 therefore selected for subjects with relatively higher minimum severity and/or frequency of psychosis at entry than in Study 012 (NPI-H+D scores ≥4 and baseline SAPS-H+D scores ≥5).

- Independent centralized and blinded ratings procedure for the primary outcome measure (Section 8.3.1.1.1).

- Nonpharmacologic, brief psychosocial therapy adapted for PD (BPST-PD) used during the 2-week screening period. Brief psychosocial therapy (BPST) had previously been shown to treat psychiatric and behavioral symptoms in Alzheimer's subjects (Ballard et al., 2009). The design of the BPST was modified with input from the first author to be more applicable in PD psychosis and to be used during study lead in. The intent of brief psychosocial therapy adapted for subjects with PD (BPST-PD) was to help subjects and their caregivers manage symptoms during the screening phase (per current standard of care) and screen out subjects who did not require pharmacological intervention. Only subjects with symptoms at baseline that were frequent and severe enough to warrant antipsychotic treatment were entered in the randomized portion of the study.

- Two-arm study and fewer number of study visits in order to minimize expectancy bias.

With these design enhancements, new Phase 3 Study 020 was initiated.

8.3 Pivotal Study 020

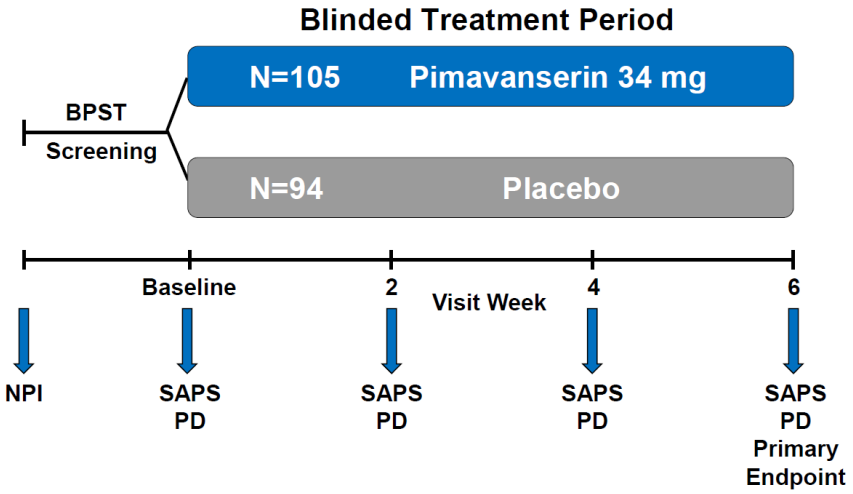
8.3.1 Pivotal Study 020 Design, Endpoints, and Statistical Analyses

8.3.1.1 Study 020 Design and Patient Population

Pivotal Study 020 was a randomized, double-blind, placebo-controlled, outpatient study that evaluated the safety and efficacy of pimavanserin 34 mg compared with placebo over a 6-week treatment period in subjects aged ≥40 years with PD psychosis. The study included a 2-week screening, 6 weeks of treatment, and a follow-up visit 4 weeks after study drug discontinuation (Figure 8–6) for those subjects who did not enroll in open-label extension Study 015. During the 2-week screening period, subjects received brief psychosocial therapy (BPST). Study 020 was conducted at 52 centers in the US and two centers in Canada, and entry criteria (see Appendix C) were consistent with the NINDS/NIMH established diagnostic criteria for PD psychosis, as published by a Movement Disorder Society task force in 2007 (Ravina et al., 2007).

Basic design of pivotal Study 020 is shown in Figure 8–6. The study design is consistent with analyses and recommendations by the FDA as described by Khin et al. (Khin et al., 2011; Khin et al., 2012).

Figure 8–6 Pivotal Study 020 – Overview of Study Design



Abbreviations: BPST = brief psychosocial therapy; NPI = Neuropsychiatric Inventory; SAPS-PD = Scale for the Assessment of Positive Symptoms in Parkinson's Disease

Nearly all subjects (98%) were on PD medications at entry; these were required to be stable from 30 days prior to study start and through the treatment period to ensure that the key secondary endpoint for motor tolerability was not confounded. In addition, prohibited and/or restricted medications included other antipsychotics and medications that could confound psychosis and/or motor assessments during the study period.

8.3.1.1.1 Study 020 Primary Endpoint SAPS-PD

The primary efficacy variable for pivotal Study 020 was the mean change from baseline to Day 43 (Week 6) on the 9-item SAPS-PD scale. The SAPS-PD measure (Voss et al., 2013) was developed for evaluation of psychotic symptoms in this patient population. The development of the SAPS-PD scale is detailed in Appendix D and summarized in Table 8–6.

The SAPS-PD scale is a 9-item scale derived from the 20-item SAPS-H+D. It captures those symptoms that are characteristic of the symptoms expressed in PD psychosis. Subjects in Study 020 were interviewed using the 20-item SAPS-H+D scale, which was also analyzed as a supportive endpoint in Study 020 and was the primary endpoint in previous trials. The responses to the 9 items of the SAPS-PD scale (Table 8–6) were then summed to provide the SAPS-PD score for that subject and visit.

Table 8–6 Scale for the Assessment of Positive Symptoms – Parkinson's Disease (SAPS-PD)

SAPS Item	
	Hallucinations
H1	Auditory hallucinations
H3	Voices conversing
H4	Somatic or tactile hallucinations
H6	Visual hallucinations
H7	Global rating of severity of hallucinations
	Delusions
D1	Persecutory delusions
D2	Delusions of jealousy
D7	Delusions of reference
D13	Global rating of severity of delusions

Each hallucination item in the SAPS-PD scale is generally scored based on frequency of the hallucination with a score of 5 corresponding to hallucinations occurring often each day; a score of 4 for occurrences almost every day; a score of 3 for at least weekly occurrences; a score of 2 for occasional hallucinations; and scores of 1 and 0 corresponding to questionable and no hallucinations of that type, respectively.

Delusional items are generally scored based on the severity of the delusion: whether a subject doubts the delusion (score of 2) or has a firm belief in the delusion (score of 3), whether the subject acts on the delusion (score of 4), or whether the delusion preoccupies a great deal of time for the subject and/or the delusion or reaction to it may be considered bizarre (score of 5).

In Study 020, the entire SAPS-H+D, and thus all nine items of the SAPS-PD ratings, were performed by central, independent, and blinded raters to minimize inter-rater variability and sources of potential bias. The ratings were obtained via real-time interviews performed over live video feeds. The rater was not on site, and did not have access to the study design, entrance criteria, visit number, treatment assignment, or any study data for the subject or caregiver. A study staff member and the subject's caregiver were present during the remote SAPS assessment. Raters scored each item of the SAPS instrument based on a standard semi-structured interview designed to elicit and evaluate the frequency and severity of each subject's symptoms (Andreasen, 1984). The score for each item of the SAPS ranges from 0 to 5.

The last item on each of the hallucinations and delusions list of items in the SAPS-PD is the "Global rating of severity" for the corresponding Hallucinations and Delusions domains, respectively. These are intended to measure the full scope of hallucinatory or delusional experiences including those assessed by individual item scores as well as any other symptoms not otherwise captured by the scale. Global ratings assessed not only the severity of the symptoms expressed but also their duration and the extent to which the subject was preoccupied with them, the degree of the subject's conviction about them, and their effects on the subject's actions. The extent to which any of the symptoms might be considered bizarre or unusual was also reflected in these ratings. The sum of severity scores was assessed with the GSAPS-H+D measure.

The SAPS-PD scale retains the reliability, sensitivity to change, and effect size of the larger SAPS-H+D, with reduced score variability. Regression analyses using the SAPS-PD scale indicated that a clinically meaningful change in the CGI-I scale was associated with a 2.33-point change in the SAPS-PD score (Voss et al., 2013).

8.3.1.1.2 Secondary Endpoints

8.3.1.1.2.1 Key Secondary Outcome Measure: Preservation of Motor Control

The key secondary endpoint was the mean change from baseline in the UPDRS Parts II+III score. This was an important safety assessment of function to assure that any antipsychotic benefit from pimavanserin did not come at the expense of motor deterioration. The UPDRS Parts II+III assessment was Investigator-rated.

The UPDRS is a comprehensive battery of motor and behavioral indices (Fahn et al., 1987). Explicit rating criteria are provided and the scale has undergone considerable testing for reliability (Goetz et al., 2008; Ondo et al., 2005; Rabey et al., 2007; Shotbolt et al., 2009; Morgante et al., 2004; Merims et al., 2006). Two domains were selected on the basis of their relevance to the intended objective for assessing motor control as a functional outcome:

- Part II: 13-item self-evaluation of the activities of daily life, including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, and cutting food
- Part III: 14-item clinician-scored motor examination

A change of approximately 5 points or greater is currently considered to be the minimal clinically important change for this measure of functional status in PD (Schrag et al., 2006; US Parkinson Study Group, 1999). A negative change in score indicates improvement, whereas a positive change in score indicates worsening of symptoms. In Study 020,

non-inferiority was concluded if the upper limit of the 95% CI for the treatment difference at Week 6 was ≤5 points.

8.3.1.1.2.2 Secondary Efficacy Measures: CGI-S and CGI-I

Secondary psychosis efficacy endpoints of Clinical Global Impression - Severity (CGI-S) and Clinical Global Impression - Improvement (CGI-I) scales were assessed by medically-qualified clinicians at the study sites. The CGI has an established history for assessing symptom severity and improvement over time (Guy, 1976). For all pimavanserin studies, the CGI-S measure was used by the Investigator to determine in a global sense the severity of psychotic symptoms in the context of the patient population. The CGI-I measure was used by the Investigator to determine how much improvement was seen at each visit and for each subject over baseline scores.

The CGI-S score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects). The CGI-I ranges from 1 (very much improved) to 7 (very much worse). Site-based investigators performed the CGI assessments.

8.3.1.1.3 Exploratory Efficacy Measures

8.3.1.1.3.1 Caregiver Burden

All Phase 2b/3 and Phase 3 studies assessed caregiver burden using the 22-item Zarit Caregiver Burden Scale (CBS) commonly used for caregivers in the dementia patient population (Zarit et al., 1980). This instrument allows quantitative assessment of burden associated with the subject's functional/behavioral impairments, the circumstances of at-home care, as well as the caregiver's health, social life, and interpersonal relations. The scale was completed in person by the primary caregiver, which in most cases was a spouse or other family member. Each of the 22 items is rated on a scale of 0 to 4, where 0 = never, 1 = rarely, 2 = sometimes, 3 = frequently, 4 = nearly always. The total score of the CBS is the sum of those 22 items.

8.3.1.1.3.2 Scales for Outcomes in Parkinson's Disease

The Phase 2/3 and Phase 3 studies of pimavanserin included assessments of nighttime sleep quality and daytime sleepiness using the Scales for Outcomes in Parkinson's Disease – Sleep (SCOPA-Sleep) scale (Marinus et al., 2003). Sleep impairment was not required for study entry. The SCOPA-Sleep is a short questionnaire consisting of separate scales that evaluate nighttime sleep quality and daytime sleepiness. It was developed for and validated in patients with PD, showing good internal consistency and reliability. The measure was completed by site staff with direct input from the subject. The Nighttime Sleep (SCOPA-NS) subscale is the sum score of 5 items, scored from 0 (not at all) to 3 (a lot [nighttime sleep

disturbed]). The Daytime Sleepiness (SCOPA-DS) subscale is the sum score of 6 items, with response options ranging from 0 (never) to 3 (often [daytime sleepiness]). The Global Nighttime Sleep subscale is a single-item, global assessment of nocturnal sleep quality using a 7-point scale (from 1 = slept very well to 7 = slept very badly).

8.3.1.1.4 Statistical Analyses

Efficacy was evaluated in Study 020 using the analysis set consisting of randomized subjects who received at least one dose of study drug and had at least one post-baseline SAPS assessment including 3 days after the last dose date. For the purpose of this briefing document, the above-defined full efficacy analysis set is labeled "modified intent-to-treat" (mITT)[3]. The "All Randomized" analysis set was also used in efficacy analyses and presentations such as for baseline characteristics, efficacy sensitivity analyses, responder analyses, etc.

Based on comments provided by the FDA following the review of the draft statistical analysis plan, mixed-model-repeated-measures (MMRM) was chosen as the primary analysis model for all numeric efficacy endpoints in Study 020. The analysis of covariance (ANCOVA) model using last observation carried forward (LOCF) was used as a sensitivity analysis and to further evaluate the robustness of the primary conclusion. Additional prespecified sensitivity analyses included:

- ANCOVA model using only observed cases (OC) without any imputation for missing data in the mITT analysis set;
- ANCOVA model using the worst observation carried forward (WOCF) method for imputing missing values in the mITT analysis set; and
- ANCOVA model using WOCF for subjects with at least 1 post-baseline result or baseline observation carried forward (BOCF) for subjects with no post-baseline results for imputing missing values in the all-randomized analysis set (WOCF/BOCF).

Additional retrospectively-defined sensitivity analyses have been conducted to further evaluate the robustness of the primary efficacy finding. These include two analyses conducted on the all-randomized analysis set using multiple imputation methodology to impute missing values. These analyses assume missing values are either missing at random (MAR) or missing values are missing not at random (MNAR). The MNAR analysis uses a

[3] In the NDA submission documents this analysis set was labeled "ITT" (intent-to-treat).

control-based pattern mixture model (PMM) method. This PMM method makes the assumption that, after drug withdrawal, the SAPS-PD scores for subjects in the pimavanserin arm follow the same trajectory as for subjects in the placebo arm. For each imputation method (MAR and MNAR), 1000 complete datasets were generated; each of which was analyzed using an ANCOVA model with effects for treatment arm and baseline SAPS-PD score. The final results were obtained by combining the least squares (LS) means and LS mean differences from these 1000 analyses using standard multiple imputation methodology (Ratitch et al., 2013).

Prespecified subgroup analyses of the primary efficacy endpoint were also conducted for each age category (<65, 65 to 75, >75 years), gender, race (white and non-white), and screening MMSE score <25 and ≥25 points. No inferential testing was performed as the study was not powered for subgroup analyses. P-values were unadjusted for multiplicity.

To compare treatment arms, the chi-square test was used for post-hoc SAPS-PD responder and CGI-I responder analyses using the All Randomized analysis set. For the purpose of these analyses, subjects with missing post-baseline values were conservatively assumed and treated as non-responders.

8.3.2 Efficacy Results for Study 020: Pivotal Phase 3 Trial

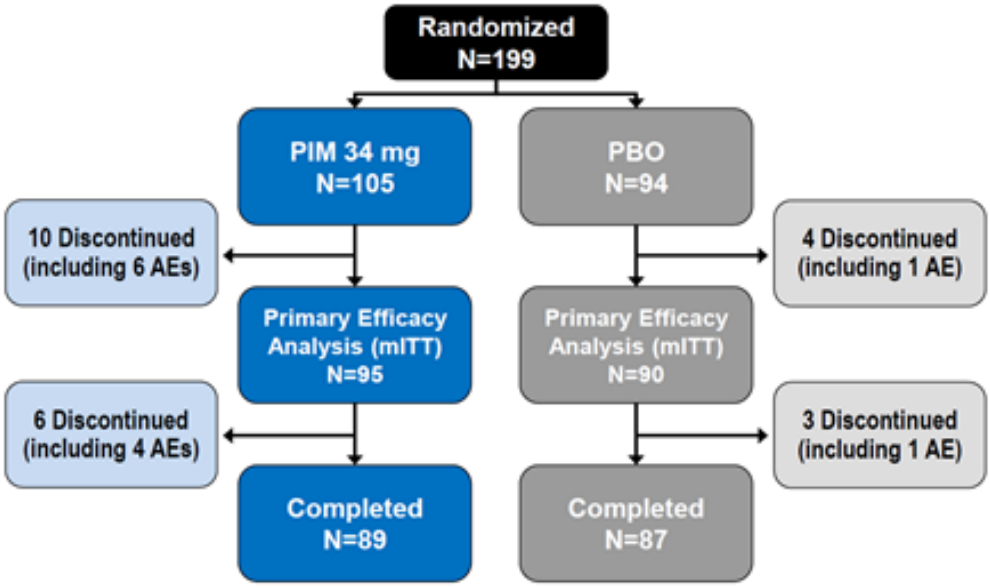
8.3.2.1 Disposition, Demographics and Baseline Characteristics

In total, 315 patients were screened of whom 116 failed screening, including 68 subjects who did not qualify for the study on the basis of screening or baseline rating scores on NPI, MMSE or SAPS scales.

Of the 199 subjects randomized, 185[4] (93%) were included in the full efficacy analysis set (mITT). One subject in the 34 mg group did not take study drug, and 13 subjects were excluded from the mITT analysis set because they did not have a baseline and at least 1 post-baseline efficacy assessment. One-hundred and seventy-six (88%) subjects completed the Week 6 visit, and of those, 171 (97%) elected to enter the long-term extension study (015) (Figure 8–7; Appendix B, Figure 1).

[4] In Study 020, of 199 randomized subjects, 14 subjects did not have a post-baseline SAPS-PD value and therefore were not included in the mITT analysis set (N=185). See Appendix B, Figure 1.

Figure 8–7 Subject Enrollment and Disposition in Study 020



Selected demographics and baseline characteristics for the All Randomized analysis set are presented in Table 8–7 and Table 8–8, respectively. There were no meaningful differences between the treatment groups for any demographic variable. Nearly all subjects (99%) were on PD medications at entry.

Table 8–7 Subject Demographics (Pivotal Study 020; All Randomized, N=199)

Demographics	PIM 34 mg (N=105)	PBO (N=94)
Age (years)		
Mean (SD)	72.7 (6.47)	72.7 (8.03)
Median (min, max)	73.0 (56, 85)	72.0 (53, 90)
Age Group, n (%)		
<65 years	12 (11.4%)	11 (11.7%)
65-75 years	56 (53.3%)	50 (53.2%)
>75 years	37 (35.2%)	33 (35.1%)
Sex, n (%)		
Male	70 (66.7%)	56 (59.6%)
Female	35 (33.3%)	38 (40.4%)
Race Group, n (%)		
White	99 (94.3%)	89 (94.7%)
Non-white	6 (5.7%)	5 (5.3%)

Table 8–8 Selected Baseline Characteristics (Pivotal Study 020; All Randomized, N=199, Mean [SEM])

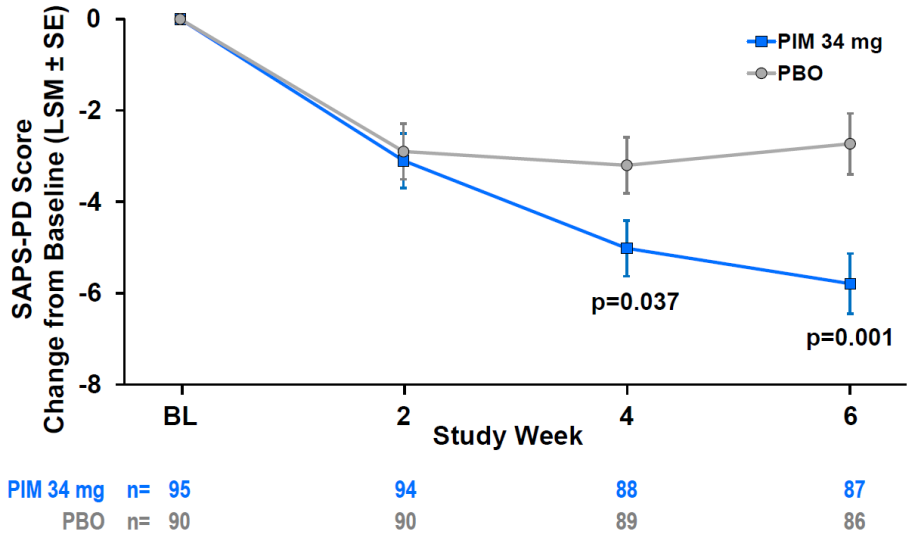
Characteristic	PIM 34 mg (N=105)	PBO (N=94)
SAPS-PD score	15.6 (0.59)	14.6 (0.58)
SAPS-H+D score	17.1 (0.73)	15.6 (0.68)
SAPS-H score	11.8 (0.50)	10.5 (0.46)
SAPS-D score	5.3 (0.42)	5.2 (0.44)
NPI-H+D score (Screening)	12.0 (0.57)	12.2 (0.55)
MMSE score (Screening)	26.0 (0.25)	26.5 (0.25)
CGI-Severity score	4.3 (0.09)	4.3 (0.09)
UPDRS II+III score	51.91 (1.69)	52.74 (1.76)
Duration of PD (months)	115.0 (7.52)	127.1 (8.16)
Duration of PD psychosis (months)	30.8 (2.87)	35.5 (4.03)

Abbreviations: SEM = standard error of the mean

8.3.2.2 Primary Efficacy Analysis

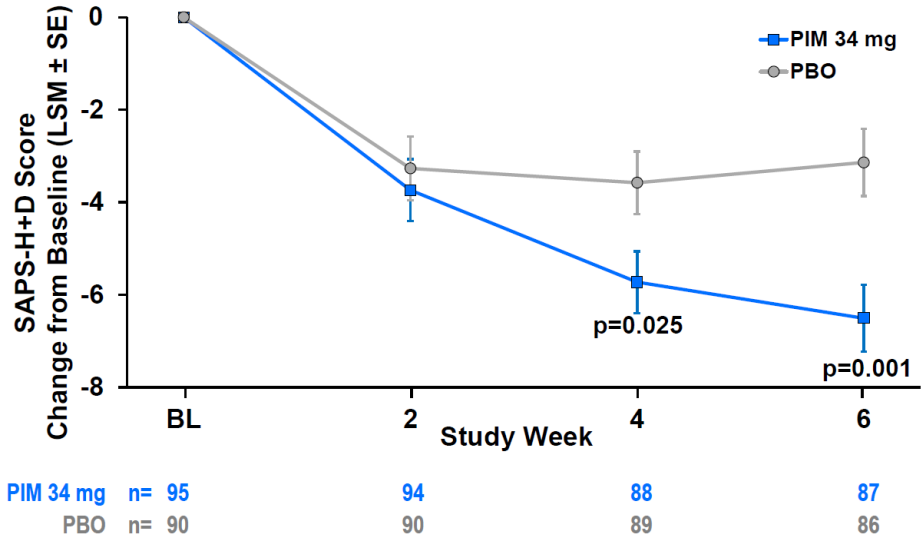
In the primary efficacy analysis, change from baseline in total SAPS-PD score was compared between two treatment arms. At the final visit (Week 6), an improvement of 5.79 points in SAPS-PD total score was observed in the pimavanserin treatment arm compared with a 2.73-point improvement observed in the placebo arm. A statistically significant treatment difference of 3.06 points in favor of pimavanserin 34 mg was demonstrated (95% CI: -4.91 to -1.20; p=0.001; effect size 0.50). The least squares (LS) mean change in SAPS-PD score from baseline to Week 6 is presented in Figure 8–8.

Figure 8–8 SAPS-PD Change from Baseline (Study 020; mITT, MMRM, N=185)



To ensure that the study primary endpoint, the 9-item SAPS-PD, had indeed captured the full and relevant spectrum of PD psychosis symptomatology, the same analysis was performed using the full 20-item SAPS-H+D scale from which the SAPS-PD was derived. The same clinically meaningful and statistically significant results were obtained with this post-hoc supportive analysis. At Week 6, the LS mean change for the pimavanserin 34 mg group was -6.51 compared to -3.14 for placebo; the treatment difference represented a 3.37-point improvement (95% CI: -5.40 to -1.35; p=0.001; effect size 0.50) (Table 8–11). The least squares (LS) mean change in SAPS-H+D score from baseline to Week 6 is presented in Figure 8–9.

Figure 8–9 SAPS-H+D Change from Baseline (Study 020; mITT, MMRM, N=185)



In addition, analysis of the change from baseline on each of the SAPS-H (hallucinations) and the SAPS-D (delusions) domain scores showed significant improvements for pimavanserin 34 mg versus placebo at Week 6. The LS mean change from baseline on Week 6 for SAPS-H was -4.18 for pimavanserin and -2.10 for placebo; the treatment difference represented an improvement of 2.08 points (95% CI: -3.46 to -0.71; p=0.003 [effect size 0.45]) and for SAPS-D was -2.28 for pimavanserin and -1.12 for placebo; with the treatment difference representing an improvement of 1.16 points (95% CI: -2.22 to -0.10; p=0.033 [effect size 0.33]).

Statistically significant improvement was observed on the sum of the two global items (Items H7 and D13) for pimavanserin 34 mg versus placebo. The LS mean change in GSAPS-H+D score from baseline to Day 43 was -1.95 for pimavanserin and -1.02 for placebo (95% CI: 1.65 to -0.21; p=0.012).

8.3.2.3 Efficacy Sensitivity Analyses

Robustness of the primary efficacy endpoint was confirmed with a number of prespecified sensitivity and supportive analyses.

Prospective sensitivity analyses to assess the robustness of the primary analysis using ANCOVA (LOCF mITT, WOCF mITT, and WOCF/BOCF in the All Randomized set) were consistent with those using MMRM and observed cases (OC MMRM), and statistical significance was achieved for pimavanserin 34 mg versus placebo in all cases (see Table 8–11).

Additional post-hoc sensitivity analyses were performed to further test for robustness of the primary efficacy results when accounting for missing data. Table 8–9 displays the number of observed and missing values for the primary endpoint at each post-baseline visit.

Table 8–9 Number of Observed and Missing Values for SAPS-PD Change from Baseline by Visit (Study 020; All Randomized)

	PIM 34 mg (N=105)		PBO (N=94)	
Study Visit	Observed	Missing	Observed	Missing
Week 2	94 (89.5%)	11 (10.5%)	90 (95.7%)	4 (4.3%)
Week 4	88 (83.8%)	17 (16.2%)	89 (94.7%)	5 (5.3%)
Week 6	87 (82.9%)	18 (17.1%)	86 (91.5%)	8 (8.5%)

We used multiple imputation methodology applied to all-randomized analysis set (Section 8.3.1.1.4).

The results of the multiple imputation analyses are presented in Table 8–10. Under the MAR assumption in the all-randomized analysis set, the treatment difference is 2.92 points (p=0.002). Under the MNAR assumption in the all-randomized analysis set, a statistically significant difference of 2.56 points was also reported (p=0.009). These analyses further demonstrate the robustness of the primary efficacy results.

Table 8–10 SAPS-PD Change from Baseline to Week 6 Sensitivity Analyses Using Multiple Imputation (Study 020; All Randomized)

Missing Data Assumption	PIM 34 mg (N=105)	PBO (N=94)
Missing at Random (MAR)		
LS Mean (SE)	-5.53 (0.643)	-2.61 (0.658)
LS Mean Difference (95% CI)	-2.92 (-4.73, -1.12)	
P-value	0.002	
Missing Not at Random (MNAR)		
LS Mean (SE)	-5.06 (0.683)	-2.51 (0.693)
LS Mean Difference (95% CI)	-2.56 (-4.46, -0.65)	
P-value	0.009	

Abbreviations: SE = standard error
Note: For the MNAR analysis, a pattern mixture model method was used. This method makes the assumption that after withdrawal, the SAPS-PD scores for subjects in the pimavanserin arm follow the same trajectory as for subjects in the placebo arm.

As presented above, multiple analytical approaches to evaluation of the primary endpoint have consistently demonstrated robustness of the observed primary efficacy results. This is presented in Table 8–11, where all sensitivity and supportive analyses yielded highly statistically significant results.

Table 8–11 Summary of Efficacy in Study 020 at Week 6: Sensitivity Analyses and Supportive Variables

Analysis Type	Measure	Rater	Population – Method[a]	LSM Treatment Δ[b]	p-value	Effect Size[c]
Sensitivity	SAPS-PD	Independent (Central)	mITT - LOCF	-2.91	0.002	-
	SAPS-PD		mITT - WOCF	-2.78	0.003	-
	SAPS-PD		All rand -WOCF/BOCF	-2.36	0.008	-
	SAPS-PD		All rand - MAR[d]	-2.92	0.002	-
	SAPS-PD		All rand - MNAR[d]	-2.56	0.009	-
Supportive	SAPS-H+D		mITT - MMRM	-3.37	0.001	0.50
	GSAPS-H+D		mITT - MMRM	-0.93	0.012	0.39
	SAPS-H		mITT - MMRM	-2.08	0.003	0.45
	SAPS-D		mITT - MMRM	-1.16	0.033	0.33

Abbreviations: ANCOVA = analysis of covariance; BOCF = baseline observation carried forward; GSAPS-H+D = sum of the global items for the H and D domains; LOCF = last-observation-carried-forward; LSM = least squares mean; MAR = missing at random; mITT = modified intent-to-treat; MMRM = mixed model repeated measures analysis; MNAR = missing not at random; N/A = not applicable; OC = observed cases; SAPS-PD = sum of 9-item PD-adapted SAPS; SAPS-D = sum of 13 items for D domain; SAPS-H = sum of 7 items for H domain; SAPS-H+D = sum of 20 items for H and D domains, WOCF = worst observation carried forward

[a] MMRM refers to OC MMRM analyses; ANCOVA was used for all LOCF, WOCF, and BOCF imputation methods.

[b] LSM treatment Δ = pimavanserin minus placebo

[c] Effect size was calculated using Cohen's *d*.

[d] Post-hoc analysis based on multiple imputation.

8.3.2.4 Secondary Efficacy Endpoints

8.3.2.4.1 Key Secondary Analysis (UPDRS Parts II+III)

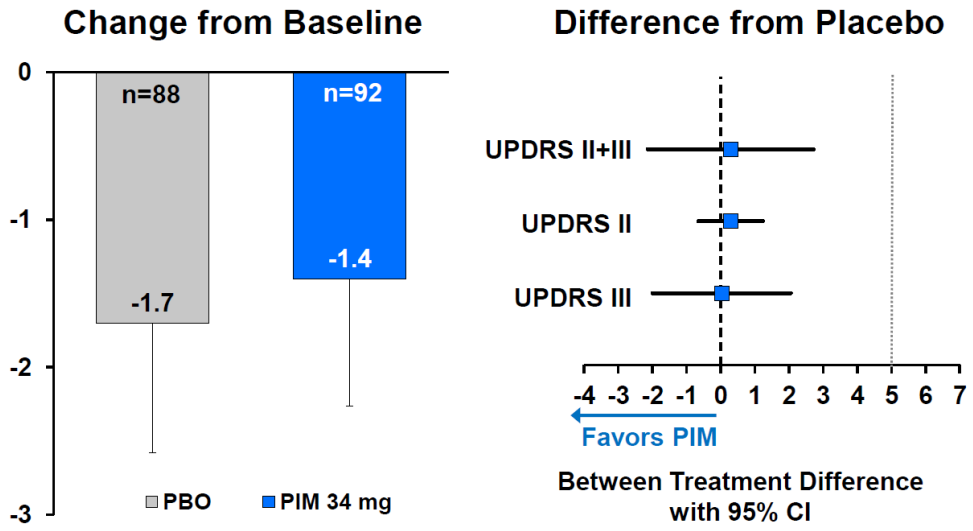
The Unified Parkinson's Disease Rating Scale (UPDRS) Parts II+III were used to assess any potential negative impact of pimavanserin on activities of daily living per UPDRS Part II and on motor symptoms of PD per UPDRS Part III and to ensure that unacceptable worsening of PD symptoms did not occur with pimavanserin treatment. As with other rating scales used in the study, a negative change in UPDRS Parts II+III total score indicates improvement whereas a positive change in score would indicate worsening of symptoms. Consistent with previous studies 006, 012, 014, changes observed in pimavanserin and placebo treatment arms remained similar. Furthermore, both groups experienced slight nominal improvement in UPDRS-Parts II+III total scores in the course of treatment (Table 8–12; Figure 8–10). Similar results were seen when UPDRS Part II and UPDRS Part III scores were analyzed separately (Figure 8–10).

Table 8–12 Combined Score for Activities of Daily Living and Motor Function (UPDRS Parts II+III) – Change from Baseline to Week 6, Study 020 (ANCOVA; OC): Modified Intent-to-Treat Analysis Set

	Pimavanserin 34 mg QD (N=95)	Placebo (N=90)
Baseline (Day 1)	n=94	n=90
Mean (SEM)	51.50 (1.81)	52.62 (1.80)
Endpoint (Week 6)	n=93	n=88
Mean (SEM)	50.07 (1.82)	50.49 (1.85)
Change from Baseline	n=92	n=88
Mean (SEM)	-1.36 (0.85)	-1.73 (0.93)
ANCOVA Model		
ANCOVA LSM (SE)	-1.40 (0.86)	-1.69 (0.88)
Difference of ANCOVA LSM (95% CI)		0.29 (-2.14, 2.72)

Possible total UPRS Parts II+III score = 0 to 108. Negative change in score indicates improvement.
Notes: Non-inferiority was concluded if the upper limit of the 95% CI for the treatment difference was ≤5 on Week 6.
Least squares mean (LSM) from ANCOVA model with treatment as a factor and baseline score as a covariate; difference between the LSM for pimavanserin and placebo (pimavanserin – placebo).

Figure 8–10 Key Secondary Outcome, UPDRS Parts II+III (Study 020; mITT, LOCF, N=185)



These results suggest that there was no clinically meaningful difference in the activities of daily living and the motor examinations of the subjects taking pimavanserin 34 mg when compared with the subjects taking placebo. This conclusion is supported by the observation that the changes from baseline in the UPDRS Parts II+III score for both pimavanserin and placebo were negative (i.e., improved).

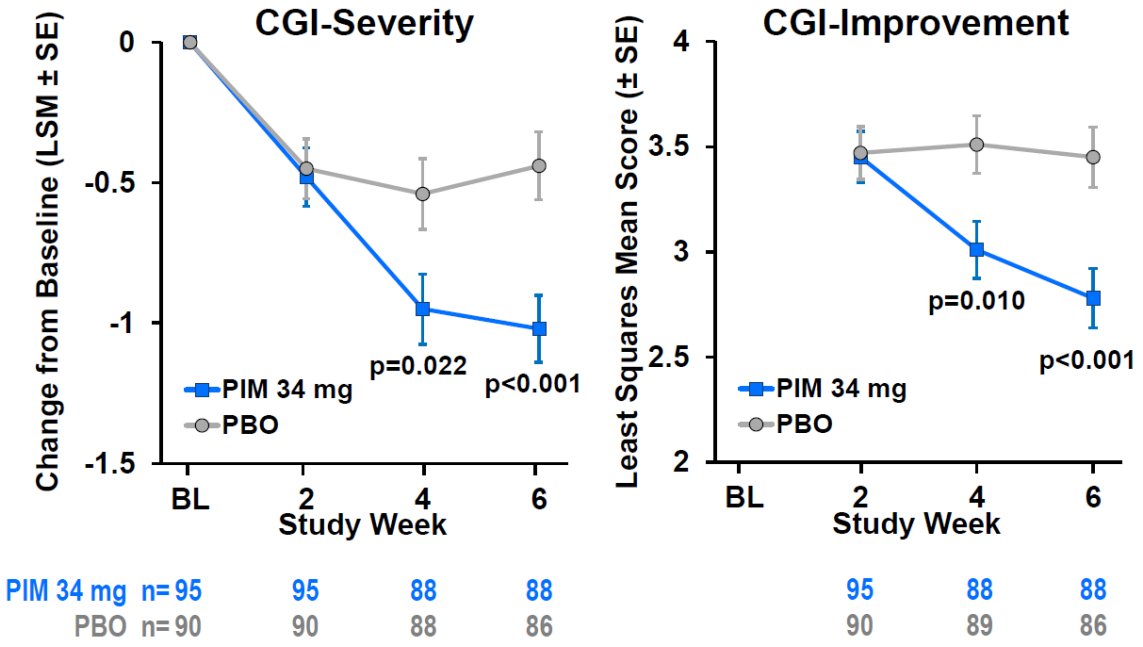
Therefore, improvements in psychotic symptoms observed with pimavanserin did not come at the expense of worsening of motor symptoms (Section 9.6.3).

8.3.2.4.2 Secondary Efficacy Endpoints – CGI-S and CGI-I

Clinical Global Impression of severity (CGI-S) of psychotic symptoms and improvement from baseline (CGI-I) were assessed by the treating clinician at the site. Statistically significant treatment effects were also noted for the pimavanserin 34 mg group for these secondary efficacy endpoints (Figure 8–11).

The efficacy observed on this clinician-assessed global measure was consistent with that seen for the central-rater-assessed SAPS measure. For CGI-S, the LS mean change from baseline on Week 6 was -1.02 for pimavanserin versus -0.44 for placebo; the treatment difference represented an improvement of 0.58 points (95% CI: -0.92 to -0.25; $p<0.001$; effect size 0.52). For CGI-I, where improvements were assessed from baseline, the LS mean at Week 6 was 2.78 for pimavanserin versus 3.45 for placebo, with the treatment difference representing an improvement of 0.67 points (95% CI: -1.06 to -0.27; $p=0.001$; effect size 0.51).

Figure 8–11 Clinical Global Impression Results (Study 020; mITT, MMRM, N=185)

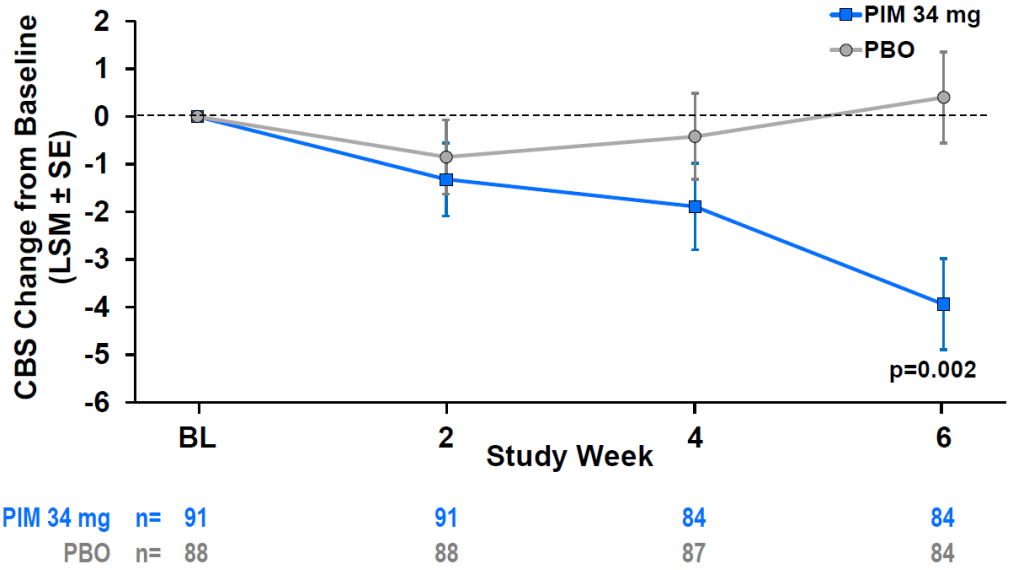


8.3.2.5 Exploratory Measures for Caregiver Burden and Sleep

8.3.2.5.1 Caregiver Burden as Measured by the 22-Item Zarit Caregiver Burden Scale

Results of the Caregiver Burden Scale (CBS) score showed a significant improvement in caregiver distress from baseline to Week 6 for the pimavanserin group over placebo. Mean (SD) baseline CBS scores were 28.71 (1.49) in the pimavanserin arm and 30.66 (1.70) in the placebo arm. At Week 6, a decrease from baseline in CBS score was observed in the pimavanserin arm, whereas an increase in burden score was observed in the placebo group; the treatment difference represented an improvement of 4.34 points (LS mean change from baseline -3.94 for pimavanserin, 0.40 for placebo; 95% CI: -7.00 to -1.67; p=0.002) (Figure 8–12). Although no single item drove the effect on caregiver burden, the item with the strongest separation was Item 16, which asked, "Do you feel that you will be unable to take care of your relative much longer?" For that question the treatment difference represented an improvement of 0.47 points (LS mean change from baseline -0.18 for pimavanserin, 0.29 for placebo; 95% CI: -0.72 to -0.22; p<0.001).

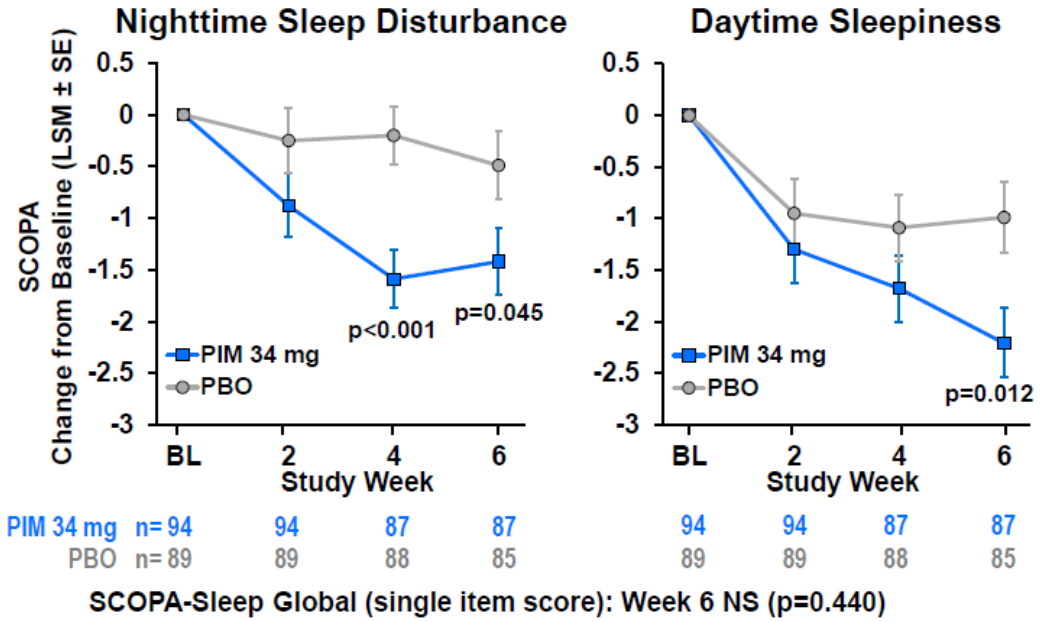
Figure 8–12 Caregiver Burden Change from Baseline (Study 020; mITT, MMRM, N=185)



8.3.2.5.2 SCOPA-Sleep Endpoints

Pimavanserin demonstrated significant improvements on the 5-item nighttime sleep score, with an LS mean (LSM) change from baseline to Week 6 of -1.42 for pimavanserin versus -0.49 for placebo; the treatment difference represented an improvement of 0.93 points (95% CI: -1.84 to -0.02; p=0.045) (Figure 8–13). At Week 6, a decrease from baseline in the single-item, SCOPA-sleep nighttime global mean score was seen for both pimavanserin 34 mg (LSM -0.38) and placebo (LSM -0.22); however, the treatment difference (pimavanserin minus placebo) was not statistically significant (-0.16; 95% CI: -0.57 to 0.25; p=0.440). For the daytime sleepiness score, the LS mean change from baseline on Week 6 was -2.21 for pimavanserin versus -0.99 for placebo, with the treatment difference representing an improvement of 1.22 points (95% CI: -2.17 to -0.27; p=0.012) (Figure 8–13).

Figure 8–13 SCOPA Nighttime Sleep Quality and Daytime Sleepiness Change from Baseline (Study 020; mITT, MMRM, N=185)



SCOPA-Sleep Global (single item score): Week 6 NS (p=0.440)

8.3.2.6 Responder Analyses

To further evaluate observed antipsychotic efficacy of pimavanserin, a number of post-hoc responder analyses were performed. Analyses were done using two different methods for defining responders: (1) Individual change in SAPS-PD score; and (2) CGI-I score categories. Using individual change in SAPS-PD score, the proportion of responders in each treatment group, based on threshold values for response ranging from a point reduction of ≥3 to ≥10, was calculated. Analyses were done on the All Randomized analyses set where subjects with missing values were counted as non-responders (Table 8–13).

Table 8–13 Response Rates Based on Change from Baseline to Week 6 in SAPS-PD (Study 020; All Randomized, N=199)

Threshold Value for Response[1]	PIM 34 mg (N=104)	Placebo (N=95)	p-value[2]
Point Reduction ≥3	62 (59.05%)	38 (40.43%)	0.009
Point Reduction ≥4	59 (56.19%)	33 (35.11%)	0.003
Point Reduction ≥5	51 (48.57%)	30 (31.91%)	0.017
Point Reduction ≥6	47 (44.76%)	29 (30.85%)	0.044
Point Reduction ≥7	39 (37.14%)	24 (25.53%)	0.079
Point Reduction ≥8	37 (35.24%)	19 (20.21%)	0.019
Point Reduction ≥9	36 (34.29%)	16 (17.02%)	0.006
Point Reduction ≥10	32 (30.48%)	15 (15.96%)	0.016

[1] Subjects with missing values were counted as non-responders.
[2] p-value is from a chi-square test.

For each value of the threshold, a subject was counted as a responder if the reduction in their SAPS-PD score was greater than or equal to the threshold value. Consistent with the overall robust efficacy observations in the study, clinically notable differences (15% to 20% difference) between pimavanserin and placebo were observed in almost all response categories. Importantly, a large individual response (delta ≥10 points) was observed in approximately one-third of pimavanserin-treated subjects, which was significantly larger than for the placebo group (30.5% vs. 16.0%, p=0.016).

Lastly, a greater proportion of subjects experienced a complete response, defined as 100% reduction in SAPS-PD score from baseline to Week 6. Complete remission of psychotic symptoms was reported in a significantly larger proportion of subjects in the pimavanserin group compared with those treated with placebo (12.4% vs. 1.1%, respectively; p=0.002 (Table 8–14). To examine long-term (1-year) outcome for these subjects (i.e., complete responders in the 6-week double blind Study 020), CGI-S status was assessed from baseline in Study 020 through Week 54 of the combined Study 020 and 015 treatment period. All of these subjects entered uncontrolled, open-label extension Study 015. They continued to experience remission of their psychotic symptoms through Week 54 of treatment, with the mean CGI-S score corresponding to overall psychotic symptoms being rated between "not at all ill" to "borderline ill" (Figure 8–14).

Figure 8–14 SAPS-PD Complete Responders: One-Year Follow-Up, CGI Severity Outcome (Study 020)

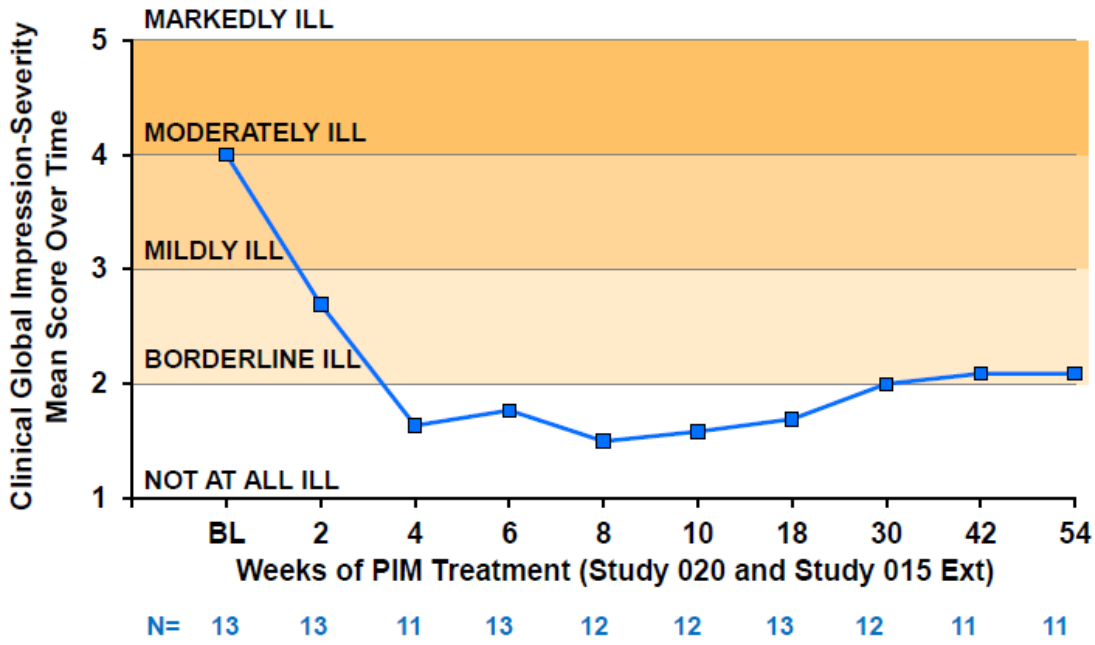
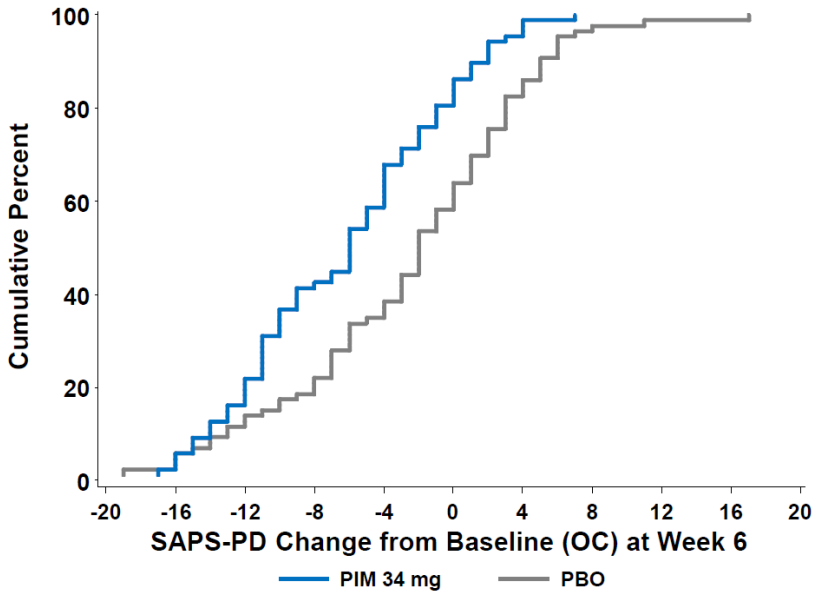


Figure 8–15 displays the cumulative distribution function (CDF) in pivotal Study 020 for the change from baseline in SAPS-PD at Week 6 (OC), for each of the two treatment groups.

Figure 8–15 Cumulative Distribution Function of Change from Baseline in SAPS-PD at Week 6 (mITT, Observed Cases, N=185)



For each value on the horizontal axis, the CDF displays the percentage of subjects with a SAPS-PD change that is less than or equal to that value (i.e., an improvement of at least that magnitude). Equivalently, the CDF displays the responder rates associated with binary thresholds determined by each value on the horizontal axis. The clear separation between the curves indicates the superiority of the pimavanserin 34 mg SAPS-PD response compared with placebo across a wide range of response thresholds.

An alternative presentation of the responder analysis is shown in Table 8–14. For the CGI-I measure, a rating of 1 (very much improved) or 2 (much improved) was used to define responders. When examined this way, a noteworthy and statistically significant difference from placebo was observed (p=0.008) (Table 8–14).

Table 8–14 Response Rates Based on SAPS-PD, SAPS-PD Complete Response, and CGI-I at Week 6 (Study 020, All Randomized, N=199)

Response Criteria[a]	PIM 34 mg (N=105)	Placebo (N=94)	p-value[b]
100% SAPS-PD Responder (score of 0 post-baseline)[d]	13 (12.4%)	1 (1.1%)	0.002
CGI-I Much or Very Much Improved[c]	43 (41.0%)	22 (23.4%)	0.008

[a] Subjects with missing values were counted as non-responders.
[b] p-value is from a chi-square test.
[c] Protocol prespecified analysis
[d] Ad-hoc analysis.

8.3.2.7 Clinical Importance and Consistency of Efficacy Results from Study 020

The efficacy of pimavanserin observed in Study 020 is strong, clinically important, and impactful with respect to subjects' functioning and wellbeing. This is reflected in three meaningful ways: (1) clinical context of the effect size observed; (2) consistency of results across multiple efficacy measures and different reporters/raters; and (3) confirmation of the results through a variety of sensitivity analyses.

8.3.2.7.1 Clinical Context of the Effect Size Observed

As discussed earlier (Section 8.3.2.6), a difference on the SAPS-PD from placebo of 3 points, experienced by nearly 60% of pimavanserin-treated subjects in Study 020, represents a difference between "severe" hallucinations and "mild" hallucinations or "marked" delusions and "questionable" delusions. Relevance of such a change for individual subject functioning and well-being is self-evident. The published estimate of 2.33 points as a clinically significant improvement (Voss et al., 2013) supports this view, and was achieved or exceeded in the All Randomized and mITT populations in Study 020, as assessed by blinded raters. Additionally, the mean effect of pimavanserin upon the investigator-assessed CGI compares favorably with effect sizes observed for most psychiatric medications and specifically most antipsychotics in clinical trials across different indications (Leucht et al., 2013). Notably, a large proportion of subjects receiving pimavanserin have experienced substantively greater improvements in their SAPS-PD and CGI scores, with a significant number experiencing total remission.

8.3.2.7.2 Consistency of Results across Multiple Efficacy Measures and Different Reporters/Raters

The totality of the efficacy demonstrated consistency of results throughout Study 020 from reports by multiple raters, including health care professionals, caregivers, and the subjects themselves. Each provides a different perspective on the subjects' underlying PD, their

psychosis, and its impact on daily life. These include the perspective of independent, central raters, blinded not only to treatment, but also to the study population, the protocol, and the visit they were rating. It also includes the perspective of the treating physicians on site who assessed the subjects' psychosis in the context of their global condition, while being blinded to the findings of the central raters. Additionally, it includes the perspective of the primary caregiver who was often a family member, untrained in medical science, but who had the unique perspective of caring for the subject for up to 24 hours a day. Lastly, the subjects themselves were central to the assessment of all measures and provided input regarding their change in level of psychosis.

A summary of primary and secondary endpoints and exploratory analyses at Week 6 is presented in Table 8–15.

Table 8–15 Summary of Efficacy in Study 020 at Week 6: Primary and Secondary Endpoints and Exploratory Analyses (mITT)

Endpoint	Measure	Rater	Population – Method[a]	LSM Treatment Δ[b]	p-value	Effect Size[d]
ANTIPSYCHOTIC EFFICACY						
Primary	SAPS-PD	Independent (Central)	mITT - MMRM	-3.06	0.001	0.50
Secondary	CGI-I	Investigator	mITT - MMRM	-0.67	0.001	0.51
	CGI-I Responder[e]		mITT - Chi-square	20.82%	0.0030[c]	N/A
	CGI-I Responder[e]		All Rand - Chi-square	17.55%	0.0084[c]	N/A
	CGI-S		mITT - MMRM	-0.58	0.001	0.52
OTHER EFFICACY						
Exploratory	SCOPA-Nighttime Sleep[f]	Investigator	mITT - MMRM	-0.93	0.045	0.31
	SCOPA-Daytime Sleepiness		mITT - MMRM	-1.22	0.012	0.39
	SCOPA-Global Nighttime Sleep[g]		mITT - MMRM	-0.16	0.440	0.12
	Caregiver Burden	Caregiver	mITT - MMRM	-4.34	0.002	0.50
OTHER						
Key secondary	UPDRS Parts II+III	Investigator	mITT - ANCOVA	0.29	-2.14, 2.72[h]	-

Abbreviations: All Rand = All Randomized; ANCOCA = analysis of covariance; LSM = least squares mean; mITT = modified intent-to-treat; MMRM = mixed model repeated measures analysis; N/A = not applicable; OC = observed cases; SAPS-PD = sum of 9-item PD-adapted SAPS

[a] MMRM refers to OC MMRM analyses.

[b] LSM treatment Δ (or difference in responders) = pimavanserin minus placebo.

[c] P-value was from a chi-square test.

[d] Effect size was calculated using Cohen's *d*.

[e] Defined as subjects with a CGI-I score of 1 (very much improved) or 2 (much improved). Subjects with missing data were considered non-responders.

[f] The Nighttime Sleep (SCOPA-NS) subscale is the sum score of 5 items, scored from 0 (not at all) to 3 (a lot [nighttime sleep disturbed]).

[g] The Global Nighttime Sleep subscale is a single-item, global assessment of nocturnal sleep quality using a 7-point scale (from 1 = slept very well to 7 = slept very badly).

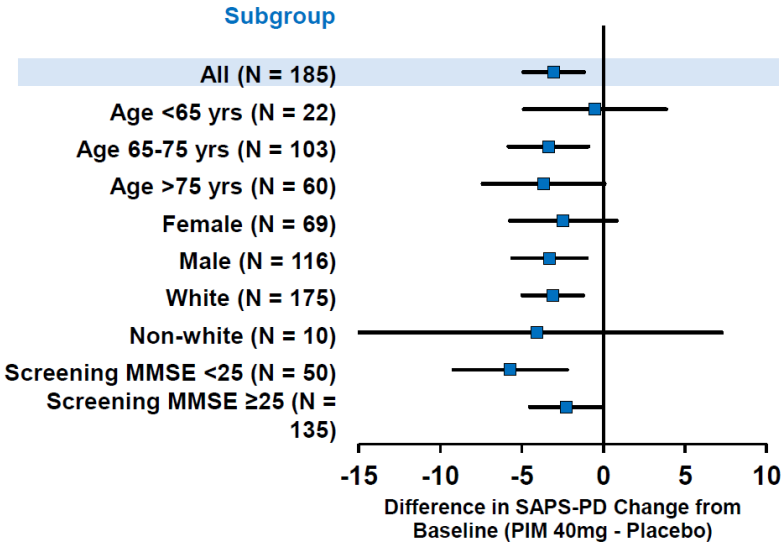
[h] 95% confidence interval.

8.3.2.7.3 Sensitivity and Confirmatory Efficacy Analyses

As discussed in the Section 8.3.2.3, a number of sensitivity and confirmatory analyses related to primary endpoint were conducted and consistently confirmed primary analysis results (see Table 8–11).

Additionally, for the purpose of evaluating the impact of key baseline parameters on the primary efficacy results, subgroup analyses were conducted. As with other analyses presented above, the subgroup analyses showed a consistency of effect of pimavanserin 34 mg over placebo regardless of subject age, gender, or baseline MMSE status (Figure 8–16).

Figure 8–16 SAPS-PD Score Change from Baseline at Week 6 (LSM with 95% CI) Across Subgroups (Study 020; mITT, OC MMRM; N=185)



Note: N represents the number of subjects in both comparison groups

8.3.2.8 Study 020 Efficacy Summary

The efficacy results of pivotal Study 020 are statistically robust and clinically meaningful, demonstrating:

- consistent and robust superiority over placebo in the primary analysis, across multiple sensitivity analyses and in different subgroups analyses;
- consistency of the results across multiple efficacy endpoints, and assessment methods and reporters; and
- the observed efficacy of pimavanserin is clinically relevant and statistically persuasive both across all efficacy measures.

8.4 Efficacy Data from the Long-Term Open-Label Studies

Two open-label extension studies (010 and 015) were conducted to assess the long-term safety and tolerability of pimavanserin in PD psychosis subjects (see Appendix B, Figure 1; note that Study 015 is ongoing). Because all subjects in long-term extension Study 015 received once daily doses of pimavanserin 34 mg, it is the focus of the following discussion.

In Study 015, subjects were required to visit the study site at Week 2 and Months 1, 3, 6, 9, 12, and every 6 months thereafter to complete safety and clinical evaluations. The studies also included efficacy assessments using the SAPS at Week 4, as well as CGI-S, CGI-I, and CBS at all timepoints. The data through Extension Week 24 were consolidated with study assessments from Studies 012, 014, and 020 to provide some information on the durability of effect in the PD psychosis population. Treatment duration in Study 015 ranged from 0.03 to 85 months, with a median of 14.9 months.

To minimize bias due to the confounding influence of drop-outs in the long-term study, the following discussion is principally focused on the data through the first 24 weeks of open-label treatment (when >75% of roll-over subjects remained on study) (Appendix B, Table 4).

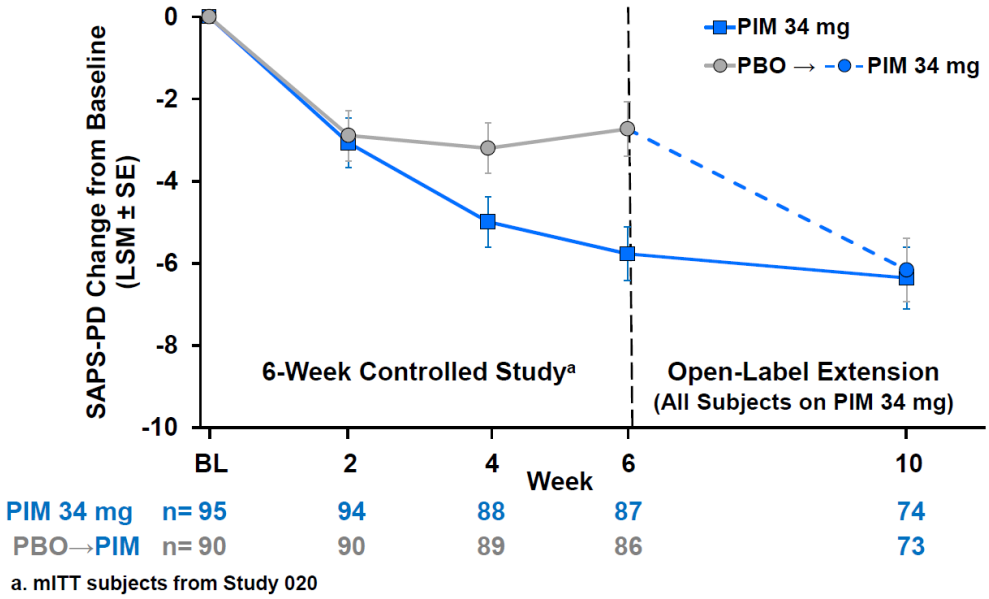
Considering the open-label nature of Study 015 and lack of control, results should be interpreted with care.

SAPS Measures

SAPS measures were evaluated through Extension Week 4 (10 weeks of total study treatment including the 6 weeks in the double-blind studies). SAPS-PD mean scores by study visits from the Study 020 are presented in Figure 8–17. Subjects were followed from baseline in the double-blind Study 020 into extension Study 015 based on their original treatment assignment in Study 20.

Here, we observed the change in SAPS-PD score for subjects who rolled into 015 from 020. Over the first 4 weeks of open-label active treatment, those previously on the 34 mg pimavanserin arm maintained their SAPS-PD improvement, whereas those who had received placebo in the double-blind study achieved improvement over 4 weeks of active treatment and “caught-up” to the pimavanserin group from double-blind study. A similar pattern was seen for SAPS-H+D, SAPS-H, and SAPS-D.

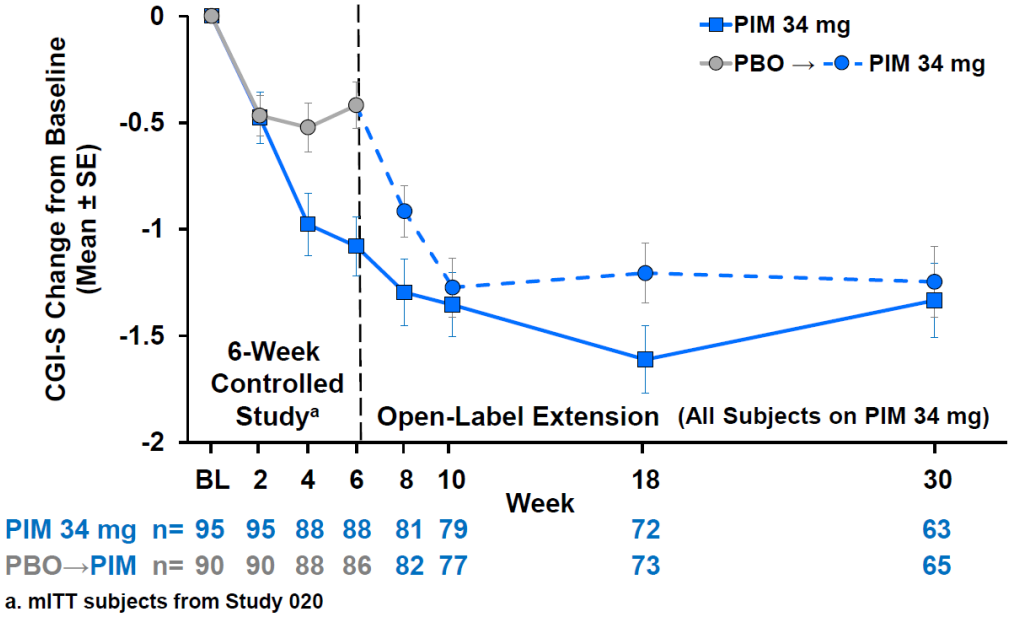
Figure 8–17 Open-Label Extension: Change in SAPS-PD Scores (Subjects Switching from Double-Blind to Open-Label Study; Study 015; N=185)



Clinical Global Impression

Results for CGI-S are presented over time through Week 24 for subjects who rolled over (Figure 8–18). For subjects who were treated with pimavanserin 34 mg in 6-week double-blind Study 020, CGI-S scores improved from -1.08 at Study 020 Week 6 to -1.33 at Extension Week 24 (i.e., following 30 weeks of treatment). The CGI-S scores for subjects treated initially with placebo improved from -0.42 at Study 020 Week 6 to -1.25 at Extension Week 24. Overall, for subjects rolling over from Study 020, the proportion of CGI-I responders (scores of 1 or 2 indicating very much improved or much improved) was 36% at Study 020 Week 6, with the proportion increasing to 53% at Extension Week 24, suggesting a possible benefit beyond Study 020 Week 6. However, approximately 25% of subjects discontinued by Week 24; therefore, results should be interpreted with caution (Figure 8-18), particularly in the absence of a parallel control group.

Figure 8–18 Open-Label Extension: Change in CGI-S Scores through 6 Months (30 weeks) of Treatment (Subjects Switching from Double-Blind to Open-Label Study; Study 015; N=185)



8.5 Pimavanserin Efficacy Conclusions

Pimavanserin 34 mg has demonstrated efficacy in the treatment of PD psychosis in a 6-week, placebo-controlled study. The strength of pimavanserin efficacy in Study 020 is defined by substantial effect size, persuasive statistical evidence, confirmatory sensitivity analyses, and consistency across multiple efficacy measures and assessors. The efficacy of pimavanserin is further supported by the data from Phase 2b/3 Studies 012 and 014. Importantly, antipsychotic efficacy was achieved without any negative impact on motor function. In addition to the observed effect on the psychotic symptoms, an overall significant benefit of pimavanserin treatment was also observed on the subject's sleep and daytime wakefulness, and on the positive impact on caregiver burden.

9 Safety Data

Safety of pimavanserin for treatment of PD psychosis was assessed in a series of clinical studies, evaluating both short-term and long-term treatment. Safety evaluations included standard adverse event (AE) monitoring; clinical laboratory parameters, electrocardiograms (ECGs), vital signs, physical examinations, and UPDRS Parts II and III assessments. Events of special interest relevant to targeted patient population or to antipsychotic therapy were also reviewed.

9.1 Overall Clinical Safety Exposure

Pimavanserin has been evaluated in 21 completed clinical studies and 4 additional studies that are currently ongoing. An estimated total of 1237 subjects have been exposed to pimavanserin (Table 9–1).

A listing of completed and ongoing clinical studies detailing number of subjects randomized to pimavanserin, study doses, and duration of treatment is presented in Appendix B, Table 1. The disposition of all PD psychosis subjects is presented in Appendix B, Figure 1.

Table 9–1 Overall Pimavanserin Exposure of Subjects (All Enrolled Subjects)

Safety Analysis Population	
PD	9
PD Psychosis	616
Healthy Subjects	276
Healthy Subjects + Adjunctive Therapy	18
Schizophrenia	177
Safety Population	**1096**
Additional Subjects Enrolled*	
ADP (Ongoing Study)	69
DDI Studies	48
NIH Studies	25
Additional Subjects	**142**
TOTAL EXPOSED	**1237****

*Additional subjects enrolled includes subjects who have either completed studies of pimavanserin or are participating in ongoing studies since the integrated database lock
**One subject who rolled over from an NIH study into a PD psychosis long-term safety study prior to the database lock is counted only once.
Note: Subjects in ongoing Studies ACP-103-025 and 026 are not included in this table.
Abbreviations: ADP = Alzheimer's disease psychosis; DDI = drug-drug interaction; NIH = National Institutes of Health; PD = Parkinson's disease

9.2 Pimavanserin Exposure in the Safety Analysis Population

The total number of subjects exposed to pimavanserin in all indications in the Safety Analysis Population including healthy volunteers, is 1096 (this figure excludes subjects treated in one ongoing study for Alzheimer's disease psychosis). As presented Table 9–2, the majority of

the subjects in the Safety Population were treated for PD psychosis (616 – this figure excludes nine subjects with PD without psychosis who were randomized to receive pimavanserin in one Phase 2 safety and tolerability study). A total of 294 healthy volunteers and 177 subjects with schizophrenia have also been exposed to pimavanserin in clinical studies.

Although the Safety Analysis Population includes a total of 1096 unique subjects, in some studies a subject could receive multiple dose levels (e.g., double-blind vs. open-label extension studies, or flexible dose studies). As a result, among those exposed to pimavanserin in the Safety Analysis Population (N=1096):

- 764 (70%) subjects received 34 mg
- 514 (47%) subjects received doses <34 mg (0.85-21 mg)
- 206 (19%) subjects received doses >34 mg (43-255 mg)

Total subject exposure in PD psychosis (n=616) exceeds 900 person-years and the longest single exposure exceeds 10 years for one subject from Study 010 who received once-daily doses of up to 51 mg pimavanserin for eight years and who rolled-over into Study 015 and then received once-daily doses of 34 mg for over an additional 2 years.

Table 9–2 Overall Numbers of Subjects by Population and Treatment Received

Population	Placebo	Pimavanserin	Active Comparator Therapy[a]	Pimavanserin-Adjunctive Therapy[a]
Safety Analysis Population	**210**	**901**	**269**	**195**
PD/PD Psychosis	64	625	0	0
PD	4	9	0	0
PD Psychosis	60	616	0	0
Schizophrenia	0	0	269	177
Healthy Volunteers	146	276	0	18

[a] Co-therapy included risperidone or haloperidol.

Subjects who participated in crossover studies were enumerated once in the pimavanserin group if received both placebo and pimavanserin.

Subjects who participated in crossover studies were enumerated once in pimavanserin-adjunctive therapy group if received both active adjunctive therapy and pimavanserin-adjunctive therapy.

Rollover subjects in 010 and 015 were counted in pimavanserin group and those subjects were not enumerated in the core studies.

One subject rolled over from Study 006 to Study 010 and then to Study 015 and was counted only once in the pimavanserin group.

9.2.1 Safety Analysis Populations

The presentation of safety data will include a summary of safety for studies in healthy subjects and in subjects with schizophrenia (Table 9–3). Detailed safety information from the

PD psychosis population will be the primary focus of the following sections. Data from PD psychosis studies were combined to form the safety analysis populations: (1) PDP6 Population (PD psychosis placebo-controlled 6-week studies) comprise subjects treated for 6 weeks with placebo or pimavanserin (at doses of 8.5, 17, or 34 mg); and (2) PDPLT Population (PD psychosis open-label, long-term studies) includes subjects who transitioned from a placebo-controlled study to one of the long-term, open-label studies 010 and 015 (see Table 9–3).

Table 9–3 Pooled Datasets for Safety Populations

Pooled Population	Description (Study Numbers)	Treatment Groups Presented
Subjects with Schizophrenia (N=177)	Schizophrenia studies (007 and 008)	Dose levels presented as in individual clinical study reports
Healthy Subjects (N=294)	Healthy volunteers studies are pooled as follows: Single-dose studies: 001, 016, and 023 Multiple-dose studies: 002, 011, 017, 018 and 024Study 009 is presented separately.	Placebo ≤17, 34, 43-68, ≥85 mg, All-PIM* Placebo + Haloperidol PIM 85 mg + Haloperidol
PDP6 (N=614)	PD psychosis placebo-controlled, 6-week studies (012, 014 and 020)	Placebo 8.5, 17, 34 mg, and All-PIM
PDPLT (N=498)	PD/PD psychosis open-label, long-term studies (010 and 015)	All-PIM

*All-PIM refers to all subjects receiving pimavanserin in the PDP6 Population, regardless of dose.

Abbreviations: PDP6 = PDP subject analysis population treated with pimavanserin for 6 weeks; PDPLT = PDP subject analysis population treated with pimavanserin in open-label, long-term studies; PIM = pimavanserin

9.3 Review of Adverse Events from the Non-PDP studies

Healthy Volunteers

Phase 1 single- and multiple-dose studies in healthy subjects were conducted over a wide dose range (single doses up to 255 mg; multiple doses up to 136 mg). In single-dose studies, the most frequent treatment-emergent adverse events (TEAEs) (>5%) were: postural dizziness, headache, somnolence and dysgeusia, dyspepsia, and nausea. In multiple-dose studies (up to 136 mg/day), the most frequent TEAEs were headache, dizziness, and nausea. Nausea and vomiting were considered dose limiting due to the severity of the events.

Pimavanserin doses of ≤34 mg generally had a low incidence of TEAEs. Compared to placebo, small increases in back pain (3.1% pimavanserin ≤17 mg vs. 2.4% placebo) and disturbance in attention (3.1% pimavanserin ≤17 mg vs. 1.2% placebo) were observed.

Two healthy subjects experienced events considered severe. One subject in the 85 mg multiple-dose group experienced nausea and vomiting that resulted in discontinuation from

the study and a second subject experienced a vasovagal episode 4 hours after receiving the initial dose of 128 mg that resolved without intervention.

Overall, safety data from clinical pharmacology studies in healthy subjects demonstrated a favorable tolerability profile consistent with pimavanserin pharmacology and supported further clinical studies in patients.

Schizophrenia Population

Two randomized, double-blind, placebo-controlled studies were conducted in subjects with schizophrenia (007 and 008).

Study 007 randomized 34 subjects on stable doses of haloperidol to adjunctive pimavanserin 51 mg/day (n=16) or placebo. The overall rates of TEAEs were similar between the pimavanserin and placebo dose groups (69% and 78%, respectively). The most frequent individual TEAEs for the pimavanserin 51 mg and placebo groups were insomnia (31.3% and 44.4%, respectively), somnolence (31.3% and 11.1%, respectively), and anxiety (12.5% and 5.6%, respectively). There were no deaths, other serious TEAEs, or TEAEs leading to discontinuation.

Study 008 randomized 412 patients receiving risperidone or haloperidol to adjunctive pimavanserin 17 mg (total n=161) or placebo for up to 6 weeks. Across treatment groups, 73.5% to 87.3% of subjects experienced at least one TEAE. The most frequently reported TEAEs were headache (18.2%), sedation (11.2%), nausea (10.9%), and agitation (16.3%). Of the TEAEs having a higher incidence (>2 percentage point difference) in either pimavanserin group (haloperidol and low-dose risperidone) compared with their respective haloperidol/placebo or risperidone/placebo groups, only somnolence, nausea, dyspepsia, diarrhea, and pain in extremity had a higher incidence in both pimavanserin groups (haloperidol and low-dose risperidone). Most of the severe TEAEs occurred in no more than 1 subject each/treatment per group. No deaths occurred in the study.

Review of the safety information from early studies in schizophrenia provided supportive evidence of the safety and tolerability of pimavanserin when used in patients with psychosis as well as initial safety information for pimavanserin when used adjunctively with other antipsychotics. No significant safety concerns have been identified from these studies.

9.4 PD Psychosis Placebo-Controlled, 6-Week Studies (PDP6 Population)

9.4.1 Demographics and Other Characteristics (PDP6 Population)

In the PDP6 Population (n=614), the mean (SD) age was 71.0 (8.23) and ~80% of the total population was over 65 years old. The majority of participants were male (64%) and were classified as White (90.7%), with 22 (9.5%) and 35 (9.1%) classified as Non-white subjects

in the placebo and All-PIM groups, respectively. Due to the small proportion of Non-white subjects, the comparison between racial groups is limited. Demographic characteristics for the PDP6 Population are summarized in Table 9–4.

Table 9–4 Demographic and Baseline Characteristics for Subjects in the PDP6 Population

	Pimavanserin				Placebo
	8.5 mg (N=140)	17 mg (N=41)	34 mg (N=202)	All-PIM (N=383)	(N=231)
Age (years)					
N	140	41	202	383	231
Mean (SD)	69.6 (8.35)	72.1 (8.15)	71.1 (7.33)	70.7 (7.83)	71.5 (8.84)
Min, Max	44, 90	53, 88	40, 85	40, 90	43, 90
Age Category (years), n (%)					
40-64	37 (26.4)	7 (17.1)	35 (17.3)	79 (20.6)	45 (19.5)
65-75	69 (49.3)	16 (39.0)	108 (53.5)	193 (50.4)	105 (45.5)
>75	34 (24.3)	18 (43.9)	59 (29.2)	111 (29.0)	81 (35.1)
Sex, n (%)					
Male	89 (63.6)	24 (58.5)	144 (71.3)	257 (67.1)	134 (58.0)
Female	51 (36.4)	17 (41.5)	58 (28.7)	126 (32.9)	97 (42.0)
BMI (kg/m^2)					
n	136	41	200	377	229
Mean (SD)	25.5 (4.99)	26.7 (3.82)	26.0 (4.59)	25.9 (4.66)	26.2 (4.95)
Min, Max	16, 42	18, 38	17, 43	16, 43	15, 52
Race, n (%)					
White	124 (88.6)	41 (100.0)	183 (90.6)	348 (90.9)	209 (90.5)
Black	2 (1.4)	0	2 (1.0)	4 (1.0)	3 (1.3)
Asian	10 (7.1)	0	11 (5.4)	21 (5.5)	12 (5.2)
Other	4 (2.9)	0	6 (3.0)	10 (2.6)	7 (3.0)
Ethnicity, n (%)					
Hispanic	3 (2.1)	0	6 (3.0)	9 (2.3)	5 (2.2)
Non-Hispanic	137 (97.9)	41 (100.0)	196 (97.0)	374 (97.7)	226 (97.8)
Race Group, n (%)					
White	124 (88.6)	41 (100.0)	183 (90.6)	348 (90.9)	209 (90.5)
Non-white	16 (11.4)	0	19 (9.4)	35 (9.1)	22 (9.5)
Area, n (%)					
North America	62 (44.3)	18 (43.9)	149 (73.9)	229 (59.8)	156 (67.5)
Europe	68 (48.6)	23 (56.1)	43 (21.3)	134 (35.0)	65 (28.1)
India	10 (7.1)	0	10 (5.0)	20 (5.2)	10 (4.3)

Abbreviations: BMI = body mass index; PIM = pimavanserin

9.4.2 Adverse Events (PDP6 Population)

9.4.2.1 Most Frequent Treatment-Emergent Adverse Events

The most frequent TEAEs (≥5%) experienced by subjects in the pimavanserin 34 mg group compared with the placebo group were fall (6.4% pimavanserin 34 mg vs. 9.1% placebo), urinary tract infection (UTI) (7.4% pimavanserin 34 mg vs. 6.9% placebo), confusional state

(5.9% pimavanserin 34 mg vs. 2.6% placebo), and nausea (6.9% pimavanserin 34 mg vs. 4.3% placebo) (Table 9–5). Falls were reported more frequently in the placebo group while the other 3 events were observed more frequently in the pimavanserin group.

Among TEAEs with a higher incidence (≥1% difference) in the pimavanserin 34 mg group compared with placebo, there was a possible dose-related increase for events of confusional state and peripheral edema, but only for peripheral edema did the drug-placebo pairwise comparison for pimavanserin 34 mg in double-blind treatment (6.9%) vs. (2.2%) show a statistically significant difference ($p<0.05$). The majority of peripheral edema events were mild in severity, with only 5 of 20 subjects (4 pimavanserin, 1 placebo) requiring diuretic treatment. There were no discontinuations due to peripheral edema.

Among the most frequent TEAEs (≥5%) in the placebo group, the comparative incidences for the pimavanserin 34 mg group were consistently lower as follows: fall (6.4% vs. 9.1%), headache (2.5% vs. 5.2%), and orthostatic hypotension (1.0% vs. 5.2%). Drug-placebo pairwise comparison of these TEAEs showed a significantly ($p<0.05$) lower incidence of orthostatic hypotension in the 34 mg pimavanserin and All-PIM groups compared with placebo.

Further discussion of orthostatic hypotension and falls can be found in Section 9.6.2.

Table 9–5 Treatment-Emergent Adverse Events Occurring in >2% of Subjects in the PDP6 Population

Preferred Term	Pimavanserin				Placebo
	8.5 mg (N=140) n (%)	17 mg (N=41) n (%)	34 mg (N=202) n (%)	All-PIM (N=383) n (%)	(N=231) n (%)
Overall	**79 (56.4)**	**21 (51.2)**	**124 (61.4)**	**224 (58.5)**	**141 (61.0)**
Fall	7 (5.0)	3 (7.3)	13 (6.4)	23 (6.0)	21 (9.1)
Urinary tract infection	5 (3.6)	1 (2.4)	15 (7.4)	21 (5.5)	16 (6.9)
Confusional state	6 (4.3)	2 (4.9)	12 (5.9)	20 (5.2)	6 (2.6)
Nausea	6 (4.3)	0 (0.0)	14 (6.9)	20 (5.2)	10 (4.3)
Dizziness	7 (5.0)	1 (2.4)	9 (4.5)	17 (4.4)	10 (4.3)
Constipation	5 (3.6)	1 (2.4)	9 (4.5)	15 (3.9)	6 (2.6)
Hallucination	3 (2.1)	2 (4.9)	10 (5.0)	15 (3.9)	7 (3.0)
Oedema peripheral	1 (0.7)	0 (0.0)	14 (6.9)[a]	15 (3.9)	5 (2.2)
Headache	6 (4.3)	0 (0.0)	5 (2.5)	11 (2.9)	12 (5.2)
Somnolence	5 (3.6)	1 (2.4)	5 (2.5)	11 (2.9)	6 (2.6)
Insomnia	2 (1.4)	3 (7.3)	5 (2.5)	10 (2.6)	7 (3.0)
Blood creatine phosphokinase increased	5 (3.6)	1 (2.4)	3 (1.5)	9 (2.3)	3 (1.3)
Diarrhoea	3 (2.1)	1 (2.4)	5 (2.5)	9 (2.3)	4 (1.7)
Fatigue	1 (0.7)	1 (2.4)	5 (2.5)	7 (1.8)	5 (2.2)
Back pain	2 (1.4)	1 (2.4)	3 (1.5)	6 (1.6)	3 (1.3)
Gait disturbance	1 (0.7)	0 (0.0)	5 (2.5)	6 (1.6)	1 (0.4)
Hypotension	1 (0.7)	2 (4.9)	3 (1.5)	6 (1.6)	2 (0.9)
Orthostatic hypotension	4 (2.9)	0 (0.0)	2 (1.0)[a]	6 (1.6)[a]	12 (5.2)
Vomiting	3 (2.1)	0 (0.0)	3 (1.5)	6 (1.6)	1 (0.4)
Contusion	0 (0.0)	1 (2.4)	4 (2.0)	5 (1.3)	5 (2.2)
Decreased appetite	3 (2.1)	1 (2.4)	1 (0.5)	5 (1.3)	3 (1.3)
Pain in extremity	2 (1.4)	1 (2.4)	2 (1.0)	5 (1.3)	0 (0.0)
Parkinson's disease	1 (0.7)	1 (2.4)	3 (1.5)	5 (1.3)	1 (0.4)
Psychotic disorder	1 (0.7)	1 (2.4)	3 (1.5)	5 (1.3)	5 (2.2)
Tremor	3 (2.1)	1 (2.4)	1 (0.5)	5 (1.3)	4 (1.7)

Table entries include TEAEs occurring in >2% of subjects in the pimavanserin or placebo subgroups of the PDP6 Population

[a] Met $p<0.05$ level of statistical significance using Fisher's Exact test by comparing AE rate for each pimavanserin group vs. placebo.

9.4.2.2 Adverse Events Leading to Discontinuation

The overall incidence of discontinuation TEAEs was 7.9% (16 subjects) for the pimavanserin 34 mg group compared with 4.3% (10 subjects) in the placebo group. The overall incidences across the double-blind pimavanserin dose groups were: 8.5 mg (6.4%), 17 mg (7.3%), and All-PIM (7.3%).

Psychiatric disorders was the system organ class (SOC) with the highest incidence of discontinuation TEAEs for both the All-PIM and placebo groups (4.5% pimavanserin 34 mg vs. 2.6% placebo), followed by Nervous system disorders (0.5% pimavanserin 34 mg vs. 0.4% placebo). TEAEs in all other SOCs occurred in ≤2 subjects per treatment arm. Among

subjects treated with pimavanserin, the most frequently reported TEAEs leading to discontinuation by Preferred Term were hallucination (2% pimavanserin 34 mg vs. 0.4% placebo), psychotic disorder (1.5% pimavanserin 34 mg vs. 0.9% placebo), and confusional state (0.5% pimavanserin 34 mg vs. 0% placebo). The majority of hallucinations leading to discontinuation occurred early in treatment.

Table 9–6 presents the frequency of TEAEs leading to discontinuation by Preferred Term and by dose.

Table 9–6 Treatment-Emergent Adverse Events Leading to Treatment Discontinuation or Study Termination by Preferred Term in the PDP6 Population (Safety Analysis Set)

	Pimavanserin				Placebo
Preferred Term	8.5 mg (N=140) n (%)	17 mg (N=41) n (%)	34 mg (N=202) n (%)	All-PIM (N=383) n (%)	(N=231) n (%)
Overall	**9 (6.4)**	**3 (7.3)**	**16 (7.9)**	**28 (7.3)**	**10 (4.3)**
Hallucination	1 (0.7)	1 (2.4)	4 (2.0)	6 (1.6)	1 (0.4)
Psychotic disorder	0 (0.0)	0 (0.0)	3 (1.5)	3 (0.8)	2 (0.9)
Confusional state	2 (1.4)	0 (0.0)	1 (0.5)	3 (0.8)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	2 (1.0)	2 (0.5)	0 (0.0)
Urinary tract infection	0 (0.0)	0 (0.0)	2 (1.0)	2 (0.5)	1 (0.4)
Delusion	1 (0.7)	1 (2.4)	0 (0.0)	2 (0.5)	0 (0.0)
Mental status changes	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	1 (0.4)
Headache	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)
Dehydration	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)
Breast cancer	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)
Pollakiuria	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)
Respiratory distress	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)
Activities of daily living impaired	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.3)	0 (0.0)
Encephalopathy	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Hypersomnia	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Lethargy	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Paraesthesia	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Parkinson's disease	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.3)	1 (0.4)
Parkinsonism	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.3)	0 (0.0)
Syncope	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Myocardial infarction	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Fall	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Hip fracture	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Delirium	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Psychiatric symptom	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Gait disturbance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arrhythmia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30 days.

Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.

Denominators for the percentages were the number of subjects in each treatment group.

9.4.2.3 Serious Adverse Events

In the PDP6 Population, the overall incidence of serious adverse events (SAEs) was 7.9% (16 subjects) for pimavanserin 34 mg compared with 3.5% (8 subjects) for placebo; the incidences for the pimavanserin dose groups were 5.7% (8 subjects) for 8.5 mg, 2.4% (1 subject) for 17 mg, and 6.5% (25 subjects) for All-PIM. SAEs are presented in Table 9–7.

The incidence of SAEs was highest in the pimavanserin 34 mg group. However, there were no discernable patterns of specific SAEs that could be associated with pimavanserin treatment. On the contrary, a broad and heterogeneous list of SAE preferred terms was observed. Review of the reported SAEs in all treatment groups indicated that the observed events are consistent with the background disease and multiple medical comorbidities characteristic of the patient population studied.

Table 9–7 Serious Treatment-Emergent Adverse Events in in the PDP6 Population

	Pimavanserin				Placebo
Preferred Term	8.5 mg (N=140) n (%)	17 mg (N=41) n (%)	34 mg (N=202) n (%)	All-PIM (N=383) n (%)	(N=231) n (%)
Overall	**8 (5.7)**	**1 (2.4)**	**16 (7.9)**	**25 (6.5)**	**8 (3.5)**
Psychotic disorder	1 (0.7)	0	2 (1.0)	3 (0.8)	0
Urinary tract infection	0	0	3 (1.5)	3 (0.8)	1 (0.4)
Fall	1 (0.7)	0	1 (0.5)	2 (0.5)	0
Hallucination	0	0	2 (1.0)	2 (0.5)	0
Mental status changes	0	0	2 (1.0)	2 (0.5)	1 (0.4)
Parkinson's disease	0	1 (2.4)	1 (0.5)	2 (0.5)	0
Sepsis	1 (0.7)	0	1 (0.5)	2 (0.5)	0
Asthenia	0	0	1 (0.5)	1 (0.3)	0
Atrial fibrillation	0	0	1 (0.5)	1 (0.3)	0
Breast cancer	0	0	1 (0.5)	1 (0.3)	0
Bronchitis	0	0	1 (0.5)	1 (0.3)	1 (0.4)
Cellulitis	1 (0.7)	0	0	1 (0.3)	0
Confusional state	0	0	1 (0.5)	1 (0.3)	0
Dehydration	0	0	1 (0.5)	1 (0.3)	0
Delusion	1 (0.7)	0	0	1 (0.3)	0
Dementia with Lewy bodies	1 (0.7)	0	0	1 (0.3)	0
Encephalopathy	1 (0.7)	0	0	1 (0.3)	0
Fatigue	0	0	1 (0.5)	1 (0.3)	0
Haemorrhoids	0	0	1 (0.5)	1 (0.3)	0
Headache	0	0	1 (0.5)	1 (0.3)	0
Hip fracture	1 (0.7)	0	0	1 (0.3)	0

Table 9–7 Serious Treatment-Emergent Adverse Events in in the PDP6 Population (Continued)

Preferred Term	Pimavanserin				Placebo
	8.5 mg (N=140) n (%)	17 mg (N=41) n (%)	34 mg (N=202) n (%)	All-PIM (N=383) n (%)	(N=231) n (%)
Overall	**8 (5.7)**	**1 (2.4)**	**16 (7.9)**	**25 (6.5)**	**8 (3.5)**
Inguinal hernia repair	1 (0.7)	0	0	1 (0.3)	0
Multi-organ failure	0	0	1 (0.5)	1 (0.3)	0
Myocardial infarction	1 (0.7)	0	0	1 (0.3)	0
Respiratory distress	0	0	1 (0.5)	1 (0.3)	0
Septic shock	0	0	1 (0.5)	1 (0.3)	0
Sleep disorder	0	0	1 (0.5)	1 (0.3)	0
Syncope	1 (0.7)	0	0	1 (0.3)	0
Anaemia	0	0	0	0	1 (0.4)
Arrhythmia	0	0	0	0	1 (0.4)
Cardio-respiratory arrest	0	0	0	0	1 (0.4)
Decubitus ulcer	0	0	0	0	1 (0.4)
Delirium	0	0	0	0	1 (0.4)
Gastroenteritis	0	0	0	0	1 (0.4)
Gastrointestinal ulcer haemorrhage	0	0	0	0	1 (0.4)
Spinal fracture	0	0	0	0	1 (0.4)
Transient ischaemic attack	0	0	0	0	1 (0.4)

MedDRA version 15.1 was used to categorize the adverse events.

A treatment-Emergent Adverse Event (TEAE) was defined as an adverse event that occurred on or after the administration of first study drug dose and before or on last dose date +30 days.

Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.

Denominators for the percentages were the number of subjects in each treatment group.

The summary table was displayed in descending order of frequency based on the "All-PIM" group.

9.4.2.4 Deaths

A total of 5 deaths occurred in all placebo-controlled PDP pimavanserin studies (Study 006, 012, 014, and 020): four in pimavanserin and one in placebo treatment group. Four of the five deaths (3 on pimavanserin and 1 on placebo) occurred during study treatment period predefined as period from first dose of study medication to 30 days post last dose of study medication. One additional death in pimavanserin group was reported outside of the treatment window, 32 days following the last dose of study medication. An 84-year-old female subject receiving pimavanserin 34 mg had cataract surgery during the study. Her last dose of study drug was 4 days prior to her admission for the cataract surgery. Post-operatively, she experienced leukocytosis and fever. Subsequently, she had hypoventilation of the right lung and was intubated. Her respiratory status continued to decline, resulting in the subject's death on Day 61 (32 days post-last dose). As the events leading to subject's

death occurred within the treatment window of 30 days post last dose of study drug, this death case was also included in the total count of deaths in placebo-controlled studies.

Fatal TEAEs are summarized in Table 9–8 for the 5 subjects who died in the placebo-controlled studies. There were a total of 4 deaths (1.0%) in the All-PIM group (1 subject in the pimavanserin 8.5 mg group, myocardial infarction; 3 subjects in the pimavanserin 34 mg group, respiratory distress, sepsis, and septic shock), and 1 subject (0.4%) in the placebo group (cardio-respiratory arrest). None of the deaths was judged by the investigator to be likely related to study drug.

Table 9–8 Adverse Events with Fatal Outcomes Experienced by Subjects in the PDP6 Studies: by System Organ Class and Preferred Term

System Organ Class Preferred Term	Pimavanserin				Placebo
	8.5 mg (N=140) n (%)	17 mg (N=41) n (%)	34 mg (N=202) n (%)	All-PIM (N=383) n (%)	(N=231) n (%)
Overall	**1 (0.7)**	**0**	**3 (1.5)**	**4 (1.0)**	**1 (0.4)**
Infections and infestations	0	0	2 (1.0)	2 (0.5)	0
Sepsis	0	0	1 (0.5)	1 (0.3)	0
Septic shock	0	0	1 (0.5)	1 (0.3)	0
Cardiac disorders	1 (0.7)	0	0	1 (0.3)	1 (0.4)
Myocardial infarction	1 (0.7)	0	0	1 (0.3)	0
Cardio-respiratory arrest	0	0	0	0	1 (0.4)
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.5)	1 (0.3)	0
Respiratory distress*	0	0	1 (0.5)	1 (0.3)	0

*AE of respiratory distress resulted in study drug discontinuation on study Day 29; Death was reported 32 days following the last dose of study medication and thus was considered off-treatment as it occurred >30 days after last dose.

A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30 days.

Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.

Denominators for the percentages were the number of subjects in each treatment group.

Subject narratives detailing all five TEAEs with fatal outcomes reported in pimavanserin placebo-controlled studies are provided in Appendix E. The small numbers of reported events make it difficult to reliably assess whether or not this suggests an association with pimavanserin treatment. A review and medical analysis of the reported deaths indicated that the observed cases were consistent with the risk factors associated with the background disease and medical comorbidities. However, the reported imbalance is an important observation that require focused review and thoughtful consideration in future pimavanserin studies and pharmacovigilance activities.

9.4.3 Clinical Laboratory Evaluations (PDP6 Population)

Chemistry

For all clinical chemistry analytes examined in the PDP6 Population, the mean changes from baseline to Week 6 were not considered clinically significant, were similar between pimavanserin and placebo groups, and did not indicate any dose-dependent effects of pimavanserin at daily doses of 8.5 to 34 mg (Table 9–9). No clinically meaningful differences were observed in chemistry analytes between the subgroups based on sex, age group, race category, or geographic area.

Table 9–9 Selected Clinical Chemistry: Mean Change from Baseline to Week 6 for Subjects in the PDP6 Population

	Pimavanserin				Placebo
	8.5 mg Mean (SD)	**17 mg** Mean (SD)	**34 mg** Mean (SD)	**All-PIM** Mean (SD)	Mean (SD)
Analyte (unit)	**(N=140)**	**(N=41)**	**(N=202)**	**(N=383)**	**(N=231)**
Liver Panel					
Alkaline phosphatase (IU/L)	n=120 -1.1 (12.81)	n=35 2.1 (11.36)	n=169 1.8 (16.01)	n=324 0.8 (14.47)	n=200 -0.9 (12.57)
ALT (IU/L)	n=120 -0.7 (8.15)	n=35 0.8 (4.49)	n=170 0.1 (7.16)	n=325 -0.1 (7.31)	n=201 0.3 (6.54)
AST (IU/L)	n=120 -0.2 (6.38)	n=35 -0.3 (5.31)	n=170 -2.3 (27.80)	n=325 -1.3 (20.54)	n=201 -0.2 (5.57)
Bilirubin (µmol/L)	n=120 -0.53 (3.097)	n=35 -0.13 (2.230)	n=170 -0.34 (3.550)	n=325 -0.39 (3.261)	n=201 0.21 (3.073)
Renal Panel					
BUN (mmol/L)	n=120 0.15 (1.608)	n=35 -0.66 (1.692)	n=170 0.08 (1.586)	n=325 0.02 (1.619)	n=201 0.22 (1.788)
Creatinine (µmol/L)	n=120 -0.93 (14.171)	n=35 -2.74 (10.138)	n=170 0.76 (12.941)	n=325 -0.24 (13.163)	n=201 2.03 (13.903)
Uric acid (µmol/L)	n=120 -2.66 (42.871)	n=35 1.43 (40.738)	n=170 7.76 (46.353)	n=325 3.23 (44.653)	n=201 2.34 (44.347)
Muscle Panel					
Creatine kinase (IU/L)	n=120 2.3 (149.30)	n=35 -17.5 (139.82)	n=170 -34.7 (252.30)	n=325 -19.2 (209.14)	n=201 14.4 (142.43)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; SD = standard deviation

Markedly abnormal overall post-baseline chemistry values for subjects with baseline values within the normal range are presented in Table 9–10. In general, few shifts from normal to markedly abnormal values were observed. No subject met the criteria for Hy's law for drug-induced liver injury (defined as subjects with any elevated alanine aminotransferase (ALT)/aspartate aminotransferase (AST) of ≥3× upper limit of normal (ULN), ALP <2×ULN, and associated with an increase in bilirubin ≥2×ULN).

Table 9–10 Markedly Abnormal Overall Post-Baseline Clinical Chemistry Values for Subjects with Baseline Values within the Normal Range in the PDP6 Population

Analyte criteria		Pimavanserin 8.5 mg n/N [a] (%)	Pimavanserin 17 mg n/N [a] (%)	Pimavanserin 34 mg n/N [a] (%)	Pimavanserin All-PIM n/N [a] (%)	Placebo n/N[a] (%)
Liver Panel						
Albumin<50% LLN		0	0	0	0	0
Alkaline Phosphatase ≥3 ULN		0	0	0	0	0
ALT ≥3 ULN		0	0	0	0	0
AST ≥3 ULN		0	0	0	0	0
Total Bilirubin ≥34.2 µmol/L		1/128 (0.8)	0	0	1/351 (0.3)	0
LDH ≥3ULN		0	0	1/183 (0.5)	1/346 (0.3)	0
Renal Panel						
BUN ≥10.71 mmol/L		2/100 (2.0)	1/25 (4.0)	3/146 (2.1)	6/271 (2.2)	12/162 (7.4)
Creatinine ≥176.8 µmol/L		0	0	1/179 (0.6)	1/329 (0.3)	0
Uric Acid: Male ≥619.5 µmol/L		0	0	0	0	0
Uric Acid: Female ≥501.5 µmol/L		0	0	1/56 (1.8)	1/119 (0.8)	0
Muscle Panel						
Creatine Kinase/ Phosphokinase ≥3 ULN		3/119 (2.5)	0	0	3/240 (1.3)	2/118 (1.7)
Electrolyte Panel						
Calcium	<2.1 mmol/L	7/135 (5.2)	2/40 (5.0)	13/189 (6.9)	22/364 (6.0)	7/226 (3.1)
	>2.875 mmol/L	0	0	0	0	0
Chloride	<90 mmol/L	0	0	0	0	0
	>115 mmol/L	0	0	0	0	1/208 (0.5)
Potassium	<3 mmol/L	1/134 (0.7)	0	0	1/364 (0.3)	0
	>5.5 mmol/L	5/134 (3.7)	0	6/189 (3.2)	11/364 (3.0)	4/219 (1.8)
Sodium	<130 mmol/L	2/135 (1.5)	0	0	2/371 (0.5)	1/225 (0.4)
	>150 mmol/L	0	0	0	0	1/225 (0.4)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; LDH = lactose dehydrogenase; LLN = lower limit of normal; ULN = upper limit of normal

[a] N = number of subjects with at least one measurement of the particular analyte with the specified baseline condition.

Note: A subject was counted only once per row. Denominators were the corresponding N value for the particular row. If a subject had at least one markedly abnormal value post-baseline, this subject was counted under "Markedly Abnormal" column.

Hematology

In the PDP6 Population, small mean changes from baseline to Week 6 in hematology analytes were observed in both the All-PIM and placebo groups. No clinically meaningful differences were observed between treatment groups, or in subgroup analyses based on sex, age group, race category, or geographic area.

Table 9–11 shows the number of subjects whose hematologic values shifted from normal at baseline to markedly abnormal post-baseline. Few markedly abnormal values were observed in the study. Differences between groups were not considered clinically meaningful.

Markedly low absolute neutrophil counts were more frequently observed in the placebo group than the All-PIM group. Importantly, no subjects experienced markedly low white blood count (WBC) in either treatment group.

Table 9–11 Markedly Abnormal Overall Post-baseline (Value at Baseline within Normal Range) Hematology Values for Subjects in the PDP6 Population

	Pimavanserin				Placebo
Analyte criteria	**8.5 mg n/N (%)**	**17 mg n/N (%)**	**34 mg n/N (%)**	**All-PIM n/N (%)**	**n/N (%)**
WBC ≤2.8 or ≥16.0 $\times 10^9$/L	0	0	0	0	0
Absolute Neutrophil Count <1.5 $\times 10^9$/L	1/129 (0.8)	0	1/189 (0.5)	2/356 (0.6)	6/220 (2.7)
Eosinophils ≥10%	0	0	0	0	0
Hematocrit: Male ≤0.37 and decrease of ≥0.03 from BL	0	1/11 (9.1)	0	1/102 (1.0)	1/62 (1.6)
Hematocrit: Female ≤0.32 and decrease of ≥0.03 from BL	0	0	2/45 (4.4)	2/103 (1.9)	1/73 (1.4)
Hemoglobin: Male ≤115 g/L	0	0	0	0	0
Hemoglobin: Female ≤95 g/L	0	0	1/53 (1.9)	1/112 (0.9)	0
Platelet Count ≤100.0 $\times 10^9$/L	0	0	1/189 (0.5)	1/359 (0.3)	1/212 (0.5)
≥700.0 $\times 10^9$/L	0	0	0	0	0

Abbreviations: BL = Baseline; N = number of subjects had at least one measurement of the particular analyte with the specified baseline condition; WBC = white blood cell count.

A subject was counted only once per row.

If a subject had at least one markedly abnormal value post-baseline, this subject was counted as markedly abnormal.

Urinalysis

In the PDP6 Population, little or no changes in mean pH and specific gravity were observed, and no clinically meaningful differences were observed between any of the subgroups based on sex, age group, race, or geographic location.

9.4.4 Vital Signs and Physical Findings (PDP6 Population)

Vital Signs

Mean changes in vital sign parameters from baseline to Week 6 were generally similar for the pimavanserin and placebo groups. No apparent dose-dependent effects were observed across pimavanserin treatment groups and there were no apparent clinically meaningful differences among subgroups based on sex, age group, race category, or geographic region.

Table 9–12 presents markedly abnormal changes from baseline in vital sign parameters. Fewer than 3.2% of subjects in any treatment group had markedly abnormal changes at their last assessment. The frequency of markedly abnormal vital sign parameters was generally similar between the All-PIM and placebo groups. Markedly abnormal systolic blood

pressures were the most frequently observed changes, reported for 10.0% of subjects with placebo and 6.9% of subjects across all pimavanserin doses.

See Section 9.6.2 for discussion of orthostatic hypotension in the clinical trials.

Table 9–12 Markedly Abnormal Changes from Baseline in Vital Sign values for Subjects in the PDP6 Population

Vital Sign Criteria Time Point	Number of Subjects (%)				
	Pimavanserin				Placebo
	8.5 mg n/N [a] (%)	17 mg n/N [a] (%)	34 mg n/N [a] (%)	All-PIM n/N [a] (%)	n/N [a] (%)
Systolic blood pressure					
≤90 and ≥20 mmHg decrease from baseline					
Overall post-baseline	6/138 (4.3)	2/41 (4.9)	18/196 (9.2)	26/375 (6.9)	23/229 (10.0)
Last assessment	1/138 (0.7)	1/41 (2.4)	6/196 (3.1)	8/375 (2.1)	7/229 (3.1)
≥180 and ≥20 mmHg increase from baseline					
Overall post-baseline	4/138 (2.9)	1/41 (2.4)	2/196 (1.0)	7/375 (1.9)	4/229 (1.7)
Last assessment	2/138 (1.4)	0	1/196 (0.5)	3/375 (0.8)	4/229 (1.7)
Diastolic blood pressure					
≤50 and ≥15 mmHg decrease from baseline					
Overall post-baseline	3/138 (2.2)	0	10/196 (5.1)	13/375 (3.5)	7/229 (3.1)
Last assessment	2/138 (1.4)	0	5/196 (2.6)	7/375 (1.9)	1/229 (0.4)
≥105 and ≥15 mmHg increase from baseline					
Overall post-baseline	2/138 (1.4)	0	3/196 (1.5)	5/375 (1.3)	1/229 (0.4)
Last assessment	0	0	0/196 (0.0)	0	0
Pulse Rate					
≤50 and ≥15 bpm decrease from baseline					
Overall post-baseline	2/138 (1.4)	0	2/196 (1.0)	4/375 (1.1)	0
Last assessment	0	0	1/196 (0.5)	1/375 (0.3)	0
≥120 and ≥15 bpm increase from baseline					
Overall post-baseline	0	1/41 (2.4)	0	1/375 (0.3)	1/229 (0.4)
Last assessment	0	1/41 (2.4)	0	1/375 (0.3)	1/229 (0.4)

[a] Denominator was the number of subjects who had at least one measurement of the particular vital sign at the time points shown in each treatment group.

9.5 PD Psychosis Open-Label, Long-Term Studies (PDPLT Population)

9.5.1 Demographics and Other Characteristics (PDPLT Population)

In the PDPLT Population (N=498), mean age was 71.2 years. Approximately 80% were over 65 years old. The mean duration of PD was >9 years; mean duration of PD psychosis was approximately 27 months.

Medical co-morbidities were common in this population (Table 9–13). Nervous system and psychiatric disorders were the most frequently affected SOCs, as expected for this study population. Other notable SOCs affected included cardiac, metabolic, and vascular disorders reported in in 33.9%, 43.4% and 57.6% of subjects, respectively; 66.7% had a history of gastrointestinal disorders; and 71.3% had prior surgical and medical procedures. Altogether,

these rates underscore significant concurrent medical conditions present in PD patients enrolled in the study.

Table 9–13 Medical History of Subjects in the PDPLT Population*

MedDRA System Organ Class (SOC) Preferred Term	Pimavanserin (N=498) n (%)
Overall	**498 (100.0)**
Nervous system disorders	**490 (98.4)**
Parkinson's disease	473 (95.0)
Somnolence	62 (12.4)
Dementia	58 (11.6)
Headache	54 (10.8)
Psychiatric disorders	**490 (98.4)**
Hallucination, visual	406 (81.5)
Delusion	302 (60.6)
Hallucination, auditory	212 (42.6)
Depression	206 (41.4)
Anxiety	139 (27.9)
Insomnia	135 (27.1)
Psychotic disorder	55 (11.0)
Surgical and medical procedures	**355 (71.3)**
Cataract operation	83 (16.7)
Appendicectomy	69 (13.9)
Hysterectomy	54 (10.8)
Cholecystectomy	50 (10.0)
Gastrointestinal disorders	**332 (66.7)**
Constipation	203 (40.8)
Gastrooesophageal reflux disease	116 (23.3)
Musculoskeletal and connective tissue disorders	**329 (66.1)**
Back pain	105 (21.1)
Osteoarthritis	104 (20.9)
Arthritis	51 (10.2)
Vascular disorders	**287 (57.6)**
Hypertension	206 (41.4)
Orthostatic hypotension	78 (15.7)
Metabolism and nutrition disorders	**216 (43.4)**
Hypercholesterolaemia	91 (18.3)
Hyperlipidaemia	68 (13.7)
Renal and urinary disorders	**215 (43.2)**
Urinary incontinence	52 (10.4)
Pollakiuria	51 (10.2)
Infections and infestations	**212 (42.6)**
Urinary tract infection	62 (12.4)
Eye disorders	**211 (42.4)**
Cataract	103 (20.7)
Injury, poisoning and procedural complications	**183 (36.7)**
Fall	84 (16.9)
Cardiac disorders	**169 (33.9)**
Coronary artery disease	62 (12.4)
General disorders and administration site conditions	**164 (32.9)**
Oedema peripheral	75 (15.1)

Table 9–13 Medical History of Subjects in the PDPLT Population* (Continued)

MedDRA System Organ Class (SOC) Preferred Term	Pimavanserin (N=498) n (%)
Reproductive system and breast disorders	**159 (31.9)**
Benign prostatic hyperplasia	98 (19.7)
Social circumstances	**152 (30.5)**
Menopause	67 (13.5)
Postmenopause	63 (12.7)
Immune system disorders	**129 (25.9)**
Drug hypersensitivity	91 (18.3)
Endocrine disorders	**69 (13.9)**
Hypothyroidism	57 (11.4)

*As recorded on the CRF page for medical history

9.5.2 Duration of Subject Participation (PDPLT Population)

Of the 498 subjects enrolled into long-term, open-label studies, more than 150 subjects remained in the study beyond 24 months. Altogether there were more than 900 patient-years of exposure in this study.

Subjects were generally allowed to continue in the long-term study as long as there was a favorable benefit-to-risk assessment, based on the subject's medical need and clinical response as judged by the investigator. In many cases, this resulted in subjects remaining in the study while medically ill, including being hospitalized or admitted to hospice care.

9.5.3 Adverse Events (PDPLT Population)

9.5.3.1 Most Frequent Treatment-Emergent Adverse Events

The most frequent TEAEs in the PDPLT analysis population were fall (29.3%), UTI (18.5%), hallucination (14.5%), decreased weight (12.4%), and confusional state (11.0%). It is difficult to interpret these incidence rates in the absence of a concurrent control group but the overall incidence appears within what would be expected for the population at study.

The time to onset of the first TEAE for subjects in the PDPLT Population is presented in Table 9–14. Mean and median times to first TEAE onset (from treatment initiation) for overall TEAEs occurring in ≥5% of subjects are presented.

Table 9–14 Time to Onset of the First TEAE Experienced by ≥5% of Subjects (in the All-PIM Group) in the PDPLT Population

	Time to First TEAE (days) Pimavanserin (N=498)		
Preferred Term	**n**	**Mean (SD)**	**Median**
Fall	146	389.7 (459.95)	233.0
Urinary tract infection	92	402.8 (422.53)	280.5
Hallucination	72	336.8 (480.00)	138.0
Weight decreased	62	504.3 (511.06)	340.5
Confusional state	55	318.1 (396.90)	165.0
Constipation	53	460.2 (479.03)	278.0
Dizziness	43	311.9 (402.51)	87.0
Oedema peripheral	43	479.2 (563.83)	195.0
Orthostatic hypotension	43	497.0 (449.16)	407.0
Depression	43	451.2 (428.07)	245.0
Anaemia	42	493.7 (433.10)	422.5
Dysphagia	42	605.8 (508.07)	451.0
Anxiety	41	441.5 (528.48)	232.0
Nausea	38	325.1 (424.45)	169.5
Contusion	38	456.8 (483.63)	293.0
Insomnia	37	287.9 (411.17)	149.0
Hypertension	36	489.1 (461.46)	303.0
Agitation	34	400.2 (584.31)	206.0
Arthralgia	34	585.4 (584.56)	516.5
Pneumonia	34	621.9 (502.47)	438.5
Dementia	34	601.3 (470.30)	513.0
Dehydration	33	669.1 (565.28)	574.0
Somnolence	33	334.8 (442.01)	94.0
Laceration	32	560.4 (513.22)	495.5
Psychotic disorder	32	500.9 (556.00)	288.0
Back pain	30	368.7 (440.89)	201.0
Parkinson's disease	30	488.0 (497.88)	386.0
Diarrhoea	25	483.3 (665.71)	271.0
Pain in extremity	25	503.8 (390.06)	434.0
Excoriation	24	713.5 (693.43)	592.5
Headache	23	216.9 (317.87)	87.0
Tremor	23	250.7 (327.22)	129.0

MedDRA version 15.1 was used to categorize the adverse events.

A Treatment-Emergent Adverse Event (TEAE) was defined as an adverse event that occurred on or after the administration of first study drug dose and before or on last dose date +30

9.5.3.2 Adverse Events Leading to Discontinuation

The incidence of discontinuation TEAEs was 28.9% (144 subjects). The most frequent discontinuation TEAEs (≥1% incidence) in the PDPLT Population were hallucination (2.2%, 11 subjects); psychotic disorder (1.8%, 9 subjects), confusional state and PD (1.4% 7 subjects each); and myocardial infarction and UTI (1.0%, 5 subjects each).

9.5.3.3 Serious Adverse Events

In the long-term safety studies, 194 (39.0%) of the 498 subjects experienced at least one SAE at some point during the study. Most of the SAEs occurred after the first 6 months of treatment. The most frequent SAEs in this population were pneumonia (3.6%), UTI (3.2%), hip fracture and aspiration pneumonia (2.4% each), dehydration (2.0%), Parkinson's disease, pulmonary embolism, and syncope (1.6% each), and mental status changes and sepsis (1.4% each).

The majority of SAEs were considered unlikely or not related to pimavanserin treatment by the investigator, but reflected the comorbidities and natural history of the underlying population. The highest incidence of SAEs was among the oldest subjects, with 52.2% of the ≥81-year olds, 38.5% of the 71-80 year olds, 27.0% among the 61-70 year olds, 10.2% of the 51-60 year olds, and none of the ≤50 year old subjects. There was, however, no pattern as to the nature and types of SAEs reported among the age groups.

9.5.3.4 Deaths Reported in Open-Label Extension Safety Studies

A total of 62 deaths were reported in the PDPLT analysis population in the open-label long-term extension studies. The most frequent TEAEs with fatal outcomes were: myocardial infarction (5 subjects, 1.0%), acute respiratory failure and pneumonia (each experienced by 4 subjects, 0.8%); cardiac arrest, cardiac failure, Parkinson's disease (worsening), and pneumonia aspiration (each experienced by 3 subjects, 0.6%); followed by acute myocardial infarction, aspiration, cardio-respiratory arrest, cardiopulmonary failure, cerebrovascular accident (CVA), death, and dementia, (each experienced by 2 subjects, 0.4%).

The overall incidence and list of TEAEs leading to death in this uncontrolled dataset is consistent with the general list of events associated with death in the overall PD and PD psychosis population, thus making it difficult to draw a clear conclusion about any causal relationship with treatment.

Consistent with the age and disease progression, the number of subjects with fatal TEAEs continued to increase in each subsequent time periods through Year 2 (Table 9–15).

Table 9–15 Time to Event: Deaths in PDP6 and PDPLT Population

Length of Treatment	Pimavanserin (n=66*)
≤6 weeks	4
>6 weeks - ≤3 months	3
>3 months - ≤6 months	6
>6 months - ≤12 months	6
>12 months - ≤18 months:	9
>18 months - ≤24 months	12
>24 months	26

* Death was reported in one subject 32 days following the last dose of study medication and was considered off-treatment; subject is not included in this table.

There were no deaths for subjects ≤60 years old, 13 deaths in subjects aged 61-70 years, 25 deaths in subjects aged 71-80 years, and 21 deaths in subjects aged ≥81 years. The nature of these events is not unusual for this age group, with the background medical conditions as described. There was no apparent pattern in the reported causes of death or in the temporal profile of events to suggest a relationship to pimavanserin.

The most commonly experienced TEAEs (≥2 subjects) with a fatal outcome by age group at death were):

- 61-70 years: myocardial infarction (2 subjects, 1.1%);
- 71-80 years: cardiac arrest, cardiac failure, pneumonia aspiration, and dementia (2 subjects each, 0.8%);
- 81-90 years: myocardial infarction, cardio-respiratory arrest, acute respiratory failure, PD, and pneumonia (2 subjects each, 2.2%).

Independent, secondary medical review of all death cases occurring in pimavanserin PD psychosis program (including placebo-controlled [short-term] and open-label [long-term] studies) was performed. It was concluded that the description and medical analysis of the reported death events was in line with causes of death reported in the literature for this patient population and did not cluster outside of the expected distribution. This also applies to the 4 deaths that occurred in the acute, placebo-controlled, double-blind studies. Similarly, the cumulative proportion of deaths over time among pimavanserin-treated patients appears consistent with the published literature. The totality of the available information does not support likely association of the reported events with pimavanserin treatment.

9.5.4 Clinical Laboratory Evaluations (PDPLT)

Chemistry and hematology

In the PDPLT Population, none of the mean changes from baseline to last assessment appeared to be clinically significant, and no clinically meaningful differences were observed in chemistry analytes between the subgroups based on sex, age group, race category, geographic area, or concomitant antipsychotic use. Similarly, no clinically meaningful differences were observed in hematology analytes between the subgroups based on sex, age group, race category, geographic area, or concomitant antipsychotic use.

The incidence of markedly abnormal overall post-baseline chemistry and hematology values for subjects with baseline values within the normal range in this population are presented in Table 9–16.

Table 9–16 Markedly Abnormal Overall Post-baseline (Value at Baseline within Normal Range) Clinical Laboratory Values for Subjects in the PDPLT Population

Analyte	Criteria	Overall Post Baseline n/N (%)
Albumin	<50% LLN	0
ALT	≥3ULN	2/480 (0.4)
AST	≥3ULN	0
Alkaline Phosphatase	≥3 ULN	0
Calcium	<2.1 mmol	58/473 (12.3)
	>2.875 mmol/L	0
Chloride	<90 mmol/L	1/447 (0.2)
	>115 mmol/L	1/447 (0.2)
Creatine Kinase/ Phosphokinase	≥3 ULN	16/432 (3.7)
LDH	≥3ULN	0
Potassium	<3 mmol/L	2/464 (0.4)
	>5.5 mmol/L	19/464 (0.4)
Total Bilirubin	≥34.2 µmol/L	2/460 (0.4)
Sodium	<130 mmol/L	2/480 (0.4)
	>150 mmol/L	3/480 (0.6)
BUN	≥10.71 mmol/L	24/338 (7.1)
Creatinine	≥176.8 µmol/L	0
Uric Acid:	Male ≥619.5 µmol/L	1/286 (0.3)
	Female ≥501.5 µmol/L	4/172 (2.3)
WBC	$\leq 2.8 \times 10^9$/L	5/434 (1.2)
	$\geq 16.0 \times 10^9$/L	4/434 (0.9)
Absolute Neutrophil Count	$< 1.5 \times 10^9$/L	11/420 (2.6)
Eosinophils	≥10%	0
Hematocrit:	Male ≤0.37 and decrease of ≥0.03 from Baseline	14/130 (10.8)
Hematocrit:	Female ≤0.32 and decrease of ≥0.03 from Baseline	11/139 (7.9)
Hemoglobin:	Male ≤115 g/L	12/211 (5.7)
	Female ≤95 g/L	2/156 (1.3)
Platelet Count	$\leq 100.0 \times 10^9$/L	4/452 (0.9)
	$\geq 700.0 \times 10^9$/L	1/452 (0.2)

Abbreviations: LLN = lower limit of normal; N = number of subjects that had at least one measurement of the particular analyte meeting criteria for markedly abnormal; ULN = upper limit of normal; WBC = white blood cell count

Urinalysis

In the PDPLT Population, little or no change in mean pH and specific gravity were observed, and no clinically meaningful differences were observed between any of the subgroups.

9.5.5 Vital Signs and Physical Findings (PDPLT)

There were no clinically significant findings in mean change from baseline on vital sign parameters.

Table 9–17 shows the rate of markedly abnormal vital sign parameters in the PDPLT Population. The most frequent markedly abnormal vital signs were decreases from baseline in systolic and diastolic blood pressure.

See Section 9.6.2 for further discussion of orthostatic hypotension in the clinical trials.

Table 9–17 Markedly Abnormal Changes from Baseline in Vital Sign Values for Subjects in the PDPLT Population

	Number of Subjects (%)[a]
Vital Sign **Criteria** **Time Point**	**PIM** **34 mg** **(N=493)**
Systolic blood pressure	
≤90 and ≥20 mmHg decrease from baseline	
Overall post-baseline	86 (17.4)
Last assessment	30 (6.1)
≥180 and ≥20 mmHg increase from baseline	
Overall post-baseline	35 (7.1)
Last assessment	10 (2.0)
Diastolic blood pressure	
≤50 and ≥15 mmHg decrease from baseline	
Overall post-baseline	57 (11.6)
Last assessment	12 (2.4)
≥105 and ≥15 mmHg increase from baseline	
Overall post-baseline	23 (0.7)
Last assessment	7 (1.4)
Pulse Rate	
≤50 and ≥15 bpm decrease from baseline	
Overall post-baseline	21 (0.3)
Last assessment	6 (1.2)
≥120 and ≥15 bpm increase from baseline	
Overall post-baseline	3 (0.6)
Last assessment	0 (0.0)

[at] The numerator for the percentages was the number of subjects with at least 1 markedly abnormal value within the specified time period and the denominator for each period was the number of subjects who had at least 1 measurement of the particular vital sign during the specified time period.

9.6 Events of Special Interest

9.6.1 Cardiac Safety

The electrocardiographic effects of pimavanserin were investigated in a thorough QT (TQT) study (Study 018) and in an analysis of the ECGs in the randomized Phase 3 studies (Studies 012, 014, and 020). Overall these investigations showed no meaningful effects of pimavanserin on heart rate, PR or QRS intervals, whereas QTc prolongation was observed at higher doses.

Thorough QT Study

In the thorough QT (TQT) study 018, a four arm parallel study design was used. Healthy subjects received one of the following blinded treatments for 20 days: pimavanserin 68 mg/day (n=72); pimavanserin 17 mg/day (n=60); moxifloxacin 400 mg capsule on Day 20 (preceded by placebo on Days 1-19; n=59); or placebo once a day (n=61). At the time the study was performed, it was thought that the likely therapeutic pimavanserin dose would be 17 mg/day, and thus 68 mg/day would have been a four-fold supratherapeutic dose.

Electrocardiograms (and concurrent PK samples) were collected in triplicate on Day -1 and Day 20 at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 23.5 hours post dose and analyzed in a blinded fashion by a core ECG laboratory (eRT, Inc.). The primary study endpoint was prespecified to be the individualized corrected-QT interval (QTcI).

The maximum studied dose (68 mg) yielded a median observed plasma concentration (Cp) of 155 ng/mL, and a median C_{max} of 197 ng/mL, which is approximately 2.5-fold higher than the median C_{max} associated with pimavanserin 34 mg/day. There was a relative paucity of Cp values at higher exposures; only 10% of all Cp values with this dose were >230 ng/mL. The C_{max} for the 17 mg dose was ~43 ng/mL.

There was not a meaningful effect on heart rate, PR, or QRS intervals. The placebo-adjusted change from baseline QTcI is shown in Table 9–18.

Table 9–18 Maximal Mean Placebo-Adjusted Change from Baseline QTcI (Delta-Delta QTcI) [Study 018])

	Pimavanserin 17 mg/day	**Pimavanserin 68 mg/day**
Maximal Mean Delta-Delta QTcI mean (upper 90% CI)	4.7 msec (6.8 msec)	13.9 msec (15.9 msec)

Outlier analysis: There was not a meaningful outlier effect. No subjects receiving pimavanserin had an absolute QTcI >480 msec or an increase from baseline >60 msec. One

subject receiving pimavanserin 68 mg/day had an increase from baseline in the QTcI of between 30 and 60 msec.

Randomized Placebo-Controlled Phase 3 Studies

The randomized, placebo-controlled Phase 3 studies analyzed were Studies 012, 014, and 020. Study designs and pimavanserin doses tested were discussed in Section 7. Studies 012 and 020 incorporated a 34 mg/day dose.

Standard 12-lead ECG tracings and PK samples were obtained at Screening, Day 1 (Baseline, prior to initial dosing), Week 1 (Studies 012 and 014 only; no PK sample), and Weeks 2, 4, and 6, generally at trough (note that the difference between C_{max} and trough is ~10%). Initially the ECGs were machine-read but after evaluating the results of the TQT study, the decision was made to have the ECGs analyzed by a core ECG laboratory. Most ECGs were available for this core laboratory review and an analysis was performed and demonstrated that there was no informative censoring. Like the TQT study, there was not a meaningful effect on heart rate, PR, or QRS intervals. The placebo-subtracted corrected QT interval using Fridericia's correction method (QTcF) data showed no meaningful effect of pimavanserin on cardiac repolarization at the 8.5 mg/day dose and a mild degree of QTcF prolongation at 34 mg/day (Table 9–19).

Table 9–19 Core Lab Analysis - Maximal Mean Placebo-Adjusted Change from Baseline QTcF (Delta-Delta QTcF) (Pooled data from Studies 012 and 020)

	Pimavanserin 8.5 mg/day (Study 012; N=66)	**Pimavanserin 34 mg/day (Pooled data from Studies 012 and 020; N=157)**
Maximal Mean Delta-Delta QTcF mean (upper 90% CI)	1.4 msec (5.6 msec)	6.9 msec (10.0 msec*)

*At Day 8, ECGs were only available in the 012 study, where the change from baseline in the QTcF was 6.1 msec (upper 90% CI of 10.9 msec).

Note: Studies 012 and 020 evaluated pimavanserin 34 mg/day

Outlier QTcF Analysis: The QTcF outlier analyses demonstrated a lack of meaningful differences in outliers with a QTcF >480 msec or an increase in QTcF >60 msec (Table 9–20). However, there was a higher incidence in the pimavanserin cohort in the QTc increase from baseline of 30 msec - 60 msec in the pimavanserin 34 mg group. This likely represents the mild-moderate QTcF prolonging effect of pimavanserin.

Table 9–20 Core Lab Analysis – QTc Outlier Analysis

	Pimavanserin		Placebo
	8.5 mg/day (N=67)	**34 mg/day (N=164)**	**(N=150)**
QTcF >480 msec (Baseline value ≤480 msec)	2 (3.0%)	4 (2.4%)	5 (3.3%)
QTcF >500 msec (Baseline value ≤500 msec)	0	1 (0.6%)	0
Increase in QTcF 30 msec-60 msec	5 (7.5%)	32 (19.5%)	11 (7.3%)
Increase in QTcF >60 msec	0	0	1 (0.7%)

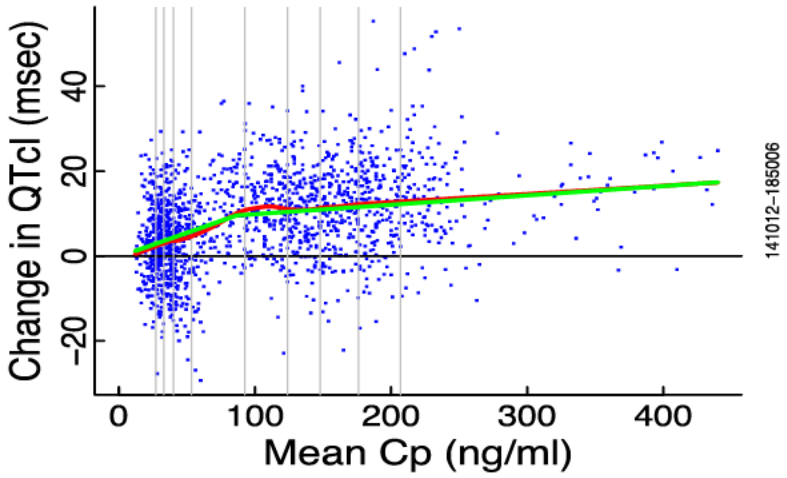
Exposure-Response Analysis

Pimavanserin exposure-response modeling was performed based on the data from the TQT study as well as the data from Phase 3 combined studies.

Thorough QT Study Exposure-Response Analysis

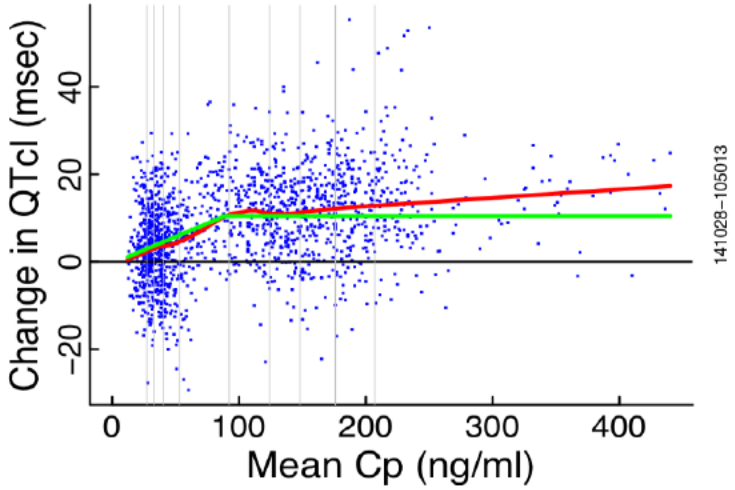
Initially, a mixed linear effects model was used to examine the PK/QTc relationship with pimavanserin, but additional exposure-response modeling demonstrated that a 2-part regression was superior in properly representing the data. Ultimately, two "optimal" models were selected. In the first of these (Figure 9–1) the right-hand slope was approximately one-fifth the left-hand slope; consistency between the smoothness of fit (smoother) through the data and the regression lines supported selection of that model. The second of these models fixed the right-hand slope to zero (Figure 9–2). This model did not differ statistically from the previous model, although graphics suggested a worsening of the fit at high Cp values. Overall, these models suggest that after a more rapid increase in the QTcI, above a threshold concentration (~86 ng/mL), a further increase in QTc is minimal or absent. Based on these models, with a daily dose of 34 mg (for which the expected Cp is ~70 ng/mL), the upper 90% CI of the increase in the QTcI is ~11 msec.

Figure 9–1 Two-part Regression Mixed Linear Effects Model: Estimated



In this model, the right-hand slope was estimated. The red line is the "smoother"; the green line is the two-part linear regression obtained from the mixed-effects model. Thin lines appear at deciles of the pimavanserin concentrations.

Figure 9–2 Two-part Regression Mixed Linear Effects Model: Fixed



In this model, the right-hand slope was fixed at zero. The red line is the "smoother"; the green line is the two-part linear regression obtained from the mixed-effects model. Thin lines appear at deciles of the pimavanserin concentrations.

Potential limitations of the exposure-response modeling are that concentrations of metabolite AC-279 (pimavanserin metabolite) were not determined and that the specific AC-279's electrophysiologic effects are not delineated. However, the TQT exposure-response model for pimavanserin, although based on pimavanserin concentrations, would include effects of both parent and metabolites. This model was used to predict the QTcI values at the

17 mg/day and 68 mg/day doses (Table 9–21) and these show an overall good correlation with the observed values in the TQT study, supporting the overall clinical relevance of the exposure-response modeling with pimavanserin.

Table 9–21 Observed Increase in QTcI at Steady State As a Result of the C_{max} Associated with a Range of Doses

Dose	Median C_{max} values obtained in the TQT study	Increase in QTcI (msec)		
		QTcI by ERT*	Model 1C	Model 1D
17	43	4.7	4.6	4.9
68*	197	13.9	12.0	10.5

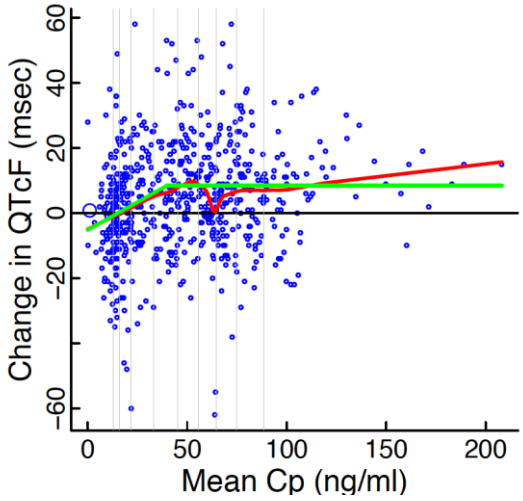
Note: Values are derived from the TQT study and PK modeling.

* These values reflect the ERT central tendency analysis (intersection union test).

Phase 3 Exposure-Response Analysis

The optimal PK/PD model used a two-part regression approach and similar to the TQT study (Study 018), demonstrated that above a plasma concentration of ~40 ng/mL (the 34 mg dose is associated with a median C_{max} of ~71 ng/mL in subjects), there was a relative plateau. In Figure 9–3, the two green lines (which meet at the cutpoint) track the smoother at all but the highest concentration values (only 2.5% of Cp values are >120 ng/mL). The model-predicted change in QTcF value from baseline for the pimavanserin 34 mg dose is the same as for the plateau -8.44 msec and the upper bound of the 90% CI is ~10 msec.

Figure 9–3 QTcF/PK Model



The red line is the "smoother"; the green line is the two-part linear regression obtained from the mixed-effects model. Thin lines appear at deciles of the pimavanserin concentrations.

Phase 3 Potential Arrhythmic Adverse Events Analysis

The occurrence of potential arrhythmic events that might represent a ventricular arrhythmia—sudden death, cardiac arrest, presyncope, and syncope—were evaluated in the AE reporting database from the pooled double-blind trials (Studies 012, 014, and 020). During the double-blind studies, there were no reported cardiac arrests or sudden deaths in subjects receiving pimavanserin, although 1 subject died of a myocardial infarction, and since the subject was found dead in bed, this likely represented a cardiac arrest; 1 subject in the placebo group had a cardio-respiratory arrest (which on review appears to be a primary cardiac arrest). Two subjects receiving pimavanserin had syncopal episodes, 1 subject receiving 8.5 mg and 1 receiving 34 mg. In 1 subject the event was documented to be due to "asystole" and was treated with a pacemaker. One subject in the placebo group had a presyncopal event. Thus there were 2 potential tachyarrhythmic events in subjects receiving pimavanserin and 2 while receiving placebo (0.52% vs 0.87% for pimavanserin compared with placebo).

In summary, pimavanserin does have a mild-to-moderate propensity to increase the QTc (central tendency upper 90% CI 10-12 msec) and may thus have a proarrhythmic risk. This can be managed through labeling and physician education as is discussed in detail below. Such an approach is commonly done for other drugs that cause a similar degree of QTc prolongation.

Based on the pimavanserin exposure-response modeling, there appears to be appears to be only minimal further QTc increases or a plateau effect at higher concentrations as demonstrated in the TQT study as well as the Phase 3 QTc exposure-response analysis. Such a relative plateau effect has been observed for other drugs (e.g., fingolimod and levomilnacipran). Pimavanserin 34 mg, the highest anticipated therapeutic dose, was predicted by the TQT study model to prolong the QTc with an upper 90% CI of ~11 msec. Importantly, in the Phase 3 study in which ECGs were evaluated after steady-state dosing, pimavanserin 34 mg/day resulted in a QTcF increase up to 10 msec (upper 90% CI) and there was not an imbalance with respect to placebo in the proportion of subjects reaching a QTc >480 msec. While 1 subject in the 34 mg pimavanserin group had a QTcF >500 msec, 1 subject in placebo had increase in QTcF >60 msec.

Ketoconazole increases steady-state pimavanserin C_{max} by ~2.9-fold. Overall in the pimavanserin development program, there is a relative paucity of matched PK/QTc data for subjects attaining the higher C_{max} (>230 ng/mL) associated with pimavanserin 34 mg/day (the recommended clinical dose) in some subjects receiving strong CYP3A4 inhibition. Thus, it is recommended that a reduced pimavanserin dose of 17 mg/day be used when moderate or strong CYP3A4 inhibitors are prescribed, resulting in a C_{max} of ~107 ng/mL. Based upon the

pimavanserin exposure-response modeling, this would be expected to yield a QTc increase similar to that observed in the Phase 3 studies and less than what was observed with the 68 mg/day dose in the TQT study (where the median C_{max} was 197 ng/mL). In addition, prescribers should be cautioned to minimize possible arrhythmic risk by not prescribing other drugs with significant potential to prolong the QT interval (particularly Class 1A and Class 3 antiarrhythmic agents); not administering pimavanserin to patients with known history of significantly prolonged QTc intervals or marked bradycardia, and preventing hypokalemia and hypomagnesemia.

9.6.1.1 CVA-Related Events

In the PDP6 Population, one subject treated with placebo experienced a SAE of "transient ischemic attack." There were no CVA-related events in the randomized, placebo-controlled studies.

In the PDPLT Population, the incidence of CVA-related events at any time during the study was 2.8% (14 subjects). Events in this category occurred only in the three oldest age groups (61 through ≥81 year olds) and comprised cerebrovascular accident (8 subjects [1.6%]), transient ischemic attack (4 subjects [0.8%]) and hemorrhagic stroke, intraventricular hemorrhage, and ischemic stroke (1 subject [0.2%] each). Cerebrovascular accidents were SAEs for 8 subjects, and for 2 of these subjects the events led to their deaths.

Excluding the transient ischemic attacks, there were a total of 10 subjects with CVA (one subject had both an ischemic stroke and a CVA). The CVA event rate per 100 patient-years is 1.1 (excluding transient ischemic attack). The Kaplan-Meier estimates for CVA event-free rates at Year 1 and Year 2 are 98.4 and 97.5, respectively.

Overall, the rates of CVA-related events appear consistent with this population's age and medical comorbidities.

9.6.2 Orthostatic Hypotension and Falls

Symptomatic orthostatic hypotension has been associated with falls, as has treatment with alpha-1 antagonists, dopamine agonists, antidepressants, and higher daily levodopa doses (Contreras and Grandas, 2012; Allen et al., 2013; Parashos et al., 2013; Adkin et al., 2003; Spindler et al., 2013; Bryant et al., 2012; Kerr et al., 2010). The risk of falls associated with these medications is compounded by the risk recently described among the broader group of elderly subjects who may also be receiving pain medications (50-75% increase in falls, same as antidepressants) as well as drugs for ulcers and gastroesophageal reflux disease, calcium, vitamin B_{12}, and some non-opioid painkillers, all of which were linked to a 15-75% increased risk of fall injuries (Kuschel et al., 2015).

Falls in PD occur at twice the frequency seen in other neurologic conditions (Allen et al., 2013) and twice the frequency seen in the general geriatric population (Voss et al., 2012). In patients with PD, injuries occur in about 25% of falls, and falls have been reported to increase the risk of hospitalization and nursing home placement (Voss et al., 2012; Temlett and Thompson, 2006; Hely et al., 2008). Notably, patients with PD have more than a doubled risk of hip fracture (Dibble and Lange, 2006).

Orthostatic Hypotension

Fewer subjects in the pimavanserin 34 mg group than in the placebo group experienced orthostatic hypotension (Table 9–22) as defined by either vital sign criteria or AE-related terms, or both in the PDP6 Population.

Vital sign criteria for orthostatic hypotension included: a decrease of ≥20 mmHg in systolic blood pressure (SBP) or a decrease of ≥15 mmHg in diastolic blood pressure (DBP), or an increase of ≥20 bpm in pulse rate (PR); each measured from 5 minutes supine to 1 minute standing at the same visit. By these vital sign criteria, 38.4% of subjects on placebo and 29.6% of subjects on pimavanserin experienced orthostatic hypotension.

The overall incidence of orthostatic hypotension-related AEs (dizziness, hypotension, orthostatic intolerance, syncope, positional vertigo, vertigo, and postural orthostatic tachycardia syndrome) was lower for the All-PIM group (8.4%) compared with the placebo group (10.4%). The majority of cases were generally mild or moderate in severity. There was no apparent increase in rates of orthostatic hypotension with increased doses of pimavanserin.

Table 9–22 TEAEs of Orthostatic Hypotension-Related Events by Preferred Term in the PDP6 Population

Special Adverse Event Category Preferred Term	Pimavanserin				Placebo
	8.5 mg (N=140) n (%)	17 mg (N=41) n (%)	34 mg (N=202) n (%)	All-PIM (N=383) n (%)	(N=231) n (%)
Orthostatic Hypotension-Related Events	**15 (10.7)**	**3 (7.3)**	**14 (6.9)**	**32 (8.4)**	**24 (10.4)**
Dizziness	7 (5.0)	1 (2.4)	9 (4.5)	17 (4.4)	10 (4.3)
Hypotension	1 (0.7)	2 (4.9)	3 (1.5)	6 (1.6)	2 (0.9)
Orthostatic hypotension	4 (2.9)	0	2 (1.0)*	6 (1.6)*	12 (5.2)
Orthostatic intolerance	2 (1.4)	0	0	2 (0.5)	0
Syncope	1 (0.7)	0	1 (0.5)	2 (0.5)	0
Vertigo positional	1 (0.7)	0	0	1 (0.3)	0
Postural orthostatic tachycardia syndrome	0	0	0	0	1 (0.4)
Vertigo	0	0	0	0	1 (0.4)

* met $p<0.05$ level of significance using Fisher's Exact test by comparing the AE rate for each pimavanserin group vs. placebo

A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30 days.

Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.

Denominators for the percentages were the number of subjects in each treatment group.

Table 9–23 summarizes the rates of orthostatic hypotension events in the PDP6 Population for the 34 mg groups and placebo groups, as defined by vital sign criteria and the specific AE of "orthostatic hypotension", separately and combined. In each case, the 34 mg group had lower rates of orthostatic hypotension-related events than the placebo group.

Table 9–23 Number (%) Subjects with Orthostatic Hypotension in the PDP6 Population

Analysis	Pimavanserin 34 mg n (%)	Placebo n (%)
Vital Signs Criteria	58/196 (29.6)	88/229 (38.4)
TEAE Preferred Term: Orthostatic Hypotension	2/202 (1.0)	12/231 (5.2)
Either of the above	58/202 (28.7)	95/231 (41.1)

In the PDPLT Population, orthostatic hypotension was reported by vital sign criteria for 46.6% of subjects, by TEAEs for 8.6% of subjects, and by either vital sign criteria or TEAEs for 47.8% of subjects. Events generally increased in incidence with increasing age. The mean time to onset for the event of orthostatic hypotension was 497.0 ± 449.2 days, with a median time to onset of 407 days (n=43).

Overall, clinical study data support the conclusion that pimavanserin is not associated with orthostatic hypotension.

Falls

Consistent with the lower rates of orthostatic hypotension in the pimavanserin groups compared to placebo, and the overall lack of negative impact on motor function, lower rates of falls were observed in pimavanserin group compared to placebo.

In the PDP6 Population, the assessment of fall-related events included the following terms: fall, ankle fracture, clavicle fracture, hip fracture, craniocerebral injury, head injury, joint dislocation, and spinal fracture. The overall incidence of TEAEs for falls-related events was lower in the pimavanserin 34 mg group (7.4%) than for the placebo group (10.0%) (Table 9–24). TEAEs of "fall" were the most frequently reported event in this category (6.0% and 9.1%, respectively). All other events were experienced by ≤1 subject per blinded treatment group with the exception of joint dislocation (2 subjects [0.9%] in the placebo group).

Table 9–24 TEAEs of Fall-Related Events by Preferred Term in the PDP6 Population

Special Adverse Event Category Preferred Term	Pimavanserin				Placebo
	8.5 mg (N=140) n (%)	17 mg (N=41) n (%)	34 mg (N=202) n (%)	All-PIM (N=383) n (%)	(N=231) n (%)
Fall-Related Events	**7 (5.0)**	**3 (7.3)**	**15 (7.4)**	**25 (6.5)**	**23 (10.0)**
Fall	7 (5.0)	3 (7.3)	13 (6.4)	23 (6.0)	21 (9.1)
Ankle fracture	0	0	1 (0.5)	1 (0.3)	0
Clavicle fracture	0	0	1 (0.5)	1 (0.3)	0
Hip fracture	1 (0.7)	0	0	1 (0.3)	1 (0.4)
Craniocerebral injury	0	0	0	0	0
Head injury	0	0	0	0	0
Joint dislocation	0	0	0	0	2 (0.9)
Spinal fracture	0	0	0	0	1 (0.4)

A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30 days.

Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.

Denominators for the percentages were the number of subjects in each treatment group.

In the PDPLT Population, the overall incidence of fall-related events was 32.3%. The majority of falls and fall-related events occurred in the 3 older age groups (61 to ≥81 years), with the highest incidence (38.9%) in the subjects aged ≥81 years.

SAEs within the group of fall-related TEAEs in the PDPLT Population were: hip fracture in 12 subjects (which also led to discontinuation in 3 subjects), fall in 5 subjects (which also led

to discontinuation for 2 subjects), femoral neck fracture and femur fracture in 4 and 3 subjects, respectively, and humerus fracture in 2 subjects.

The lower rate of falls in the pimavanserin group compared to placebo further supports the potential benefit of pimavanserin in the treatment of patients with PD psychosis.

9.6.3 Parkinson's Disease Motor Symptoms

Drug-drug interaction study with carbidopa-levodopa

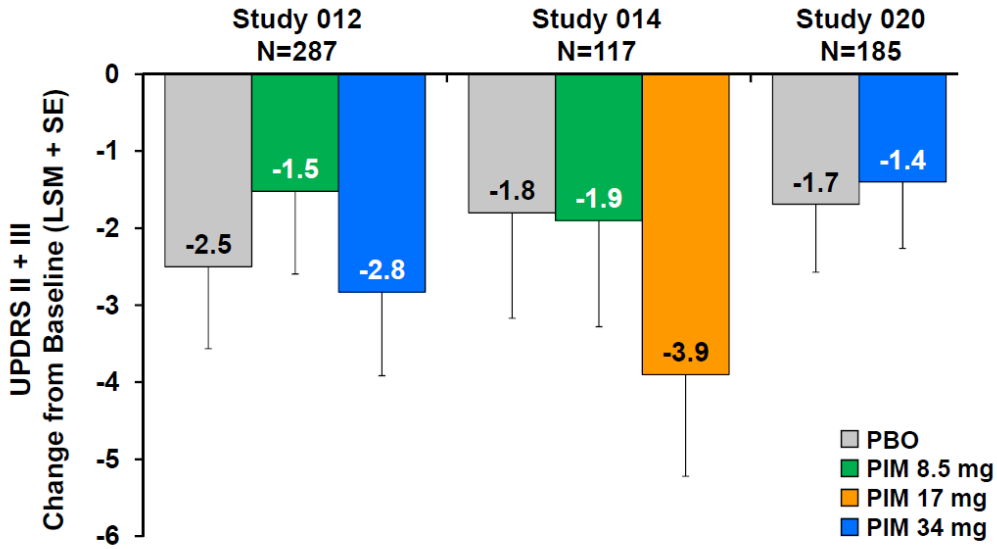
Prior to the Phase 3 program, a drug-drug interaction study with carbidopa/levodopa was conducted in healthy volunteers, demonstrating that pimavanserin has no effect on levodopa blood levels when co-administered with carbidopa/levodopa (Sinemet®). This study concluded that dose adjustments of carbidopa/levodopa are not considered necessary when administering pimavanserin (see Section 6.2).

UPDRS Parts II and III

During the Phase 3 program, the UPDRS Parts II+III scale was used to assess the effects of pimavanserin on Parkinson's motor symptoms.

In the PDP6 Population, small negative mean changes (improvement) from baseline to the last on-study observation were reported for pimavanserin and placebo groups (Figure 9–4). In prespecified analyses, pimavanserin was non-inferior to placebo on the UPDRS Parts II+III total score at all doses tested.

Figure 9–4 Change from Baseline in UPDRS Scores in the PDP6 Population (Parts II+III)



Least square means (LSM) and standard errors (SE) from ANCOVA model with treatment and region (Studies 012 and 014) as factors and baseline as a covariate at Week 6 (Studies 012, 014, and 020).

Many antipsychotic medications are associated with extrapyramidal symptoms (akathisia, dyskinesia, dystonia, and parkinsonian symptoms). Antipsychotics are also known to worsen motor symptoms in patients with Parkinson's disorder. Therefore, an assessment of extrapyramidal events was conducted in the PD psychosis program.

In the PDP6 Population, few subjects experienced extrapyramidal symptom related events (Table 9–25). None of the events of dyskinesia or dystonia were SAEs or led to discontinuation of study drug or withdrawal from the study.

Table 9–25 TEAEs of Extrapyramidal Symptom-Related Events by Preferred Term in the PDP6 Population

Special Adverse Event Category / Preferred Term	Pimavanserin				Placebo
	8.5 mg (N=140)	17 mg (N=41)	34 mg DB (N=202)	All-PIM (N=383)	(N=231)
	n (%)	n (%)	n (%)	n (%)	n (%)
Extrapyramidal Symptom-Related Events	**1 (0.7)**	**0**	**2 (1.0)**	**3 (0.8)**	**4 (1.7)**
Dyskinesia	0	0	2 (1.0)	2 (0.5)	4 (1.7)
Dystonia	1 (0.7)	0	0	1 (0.3)	0

A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30 days.

Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.

Denominators for the percentages were the number of subjects in each treatment group.

In the PDPLT Population, the overall incidence of extrapyramidal symptom-related events was 4.6% and comprised TEAEs of dyskinesia (4.0%) and dystonia (1.2%). None of the events of dyskinesia or dystonia were SAEs or led to discontinuation of study drug or withdrawal from the study.

Collectively, these data support that pimavanserin does not worsen motor symptoms in Parkinson's patients. Pimavanserin treatment can therefore be initiated without prior adjustment of Parkinson's medications, and these medications can be adjusted as needed during pimavanserin treatment.

9.6.4 Seizures/Convulsions

There were no reports of convulsion related events in the double-blind, placebo-controlled studies. In the long-term studies, convulsion TEAEs were experienced by 3 subjects (0.6%), none of which were considered related to study treatment.

9.6.5 Leukopenia/Agranulocytosis

In the PDP6 Population, low absolute neutrophil counts were observed for 2 pimavanserin-treated subjects (1 each in the 8.5 mg and 34 mg groups) and 6 subjects in the placebo group (Table 9–26). Mean change from baseline were similar in the pimavanserin and placebo groups. No subjects in any treatment group experienced markedly low WBC laboratory levels.

Table 9–26 Number (%) Subjects with Low Absolute Neutrophil Counts in the PDP6 Population

	Pimavanserin				Placebo
Analyte criteria	8.5 mg n/N (%)	17 mg n/N (%)	34 mg n/N (%)	All-PIM n/N (%)	n/N (%)
WBC ≤2.8 or ≥16.0 $\times 10^9$/L	0	0	0	0	0
Absolute Neutrophil Count <1.5 $\times 10^9$/L	1/129 (0.8)	0	1/189 (0.5)	2/356 (0.6)	6/220 (2.7)

WBC = white blood cell count

In the PDP6 Population, the overall incidences of blood dyscrasia-related events were 1.5% for the pimavanserin 34 mg group compared with 2.2% for placebo (Table 9–27). There were no events related to leukopenia, neutropenia, or agranulocytosis reported across pimavanserin groups.

Table 9–27 TEAEs of Blood Dyscrasia-Related Events by Preferred Term in the PDP6 Population

Special Adverse Event Category Preferred Term	Pimavanserin				Placebo
	8.5 mg (N=140)	17 mg (N=41)	34 mg (N=202)	All-PIM (N=383)	(N=231)
	n (%)	n (%)	n (%)	n (%)	n (%)
Blood Dyscrasia Related Events	**1 (0.7)**	**0**	**3 (1.5)**	**4 (1.0)**	**5 (2.2)**
Anaemia	1 (0.7)	0	3 (1.5)	4 (1.0)	2 (0.9)
Leukopenia	0	0	0	0	1 (0.4)
Lymphopenia	0	0	0	0	1 (0.4)
Neutrophil count decreased	0	0	0	0	1 (0.4)
Pancytopenia	0	0	0	0	0
White blood cell count decreased	0	0	0	0	1 (0.4)

A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30 days.

Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.

Denominators for the percentages were the number of subjects in each treatment group.

In the PDPLT Population, few subjects experienced low WBC or low absolute neutrophil counts in the open-label studies. Overall, there was no indication that pimavanserin contributed to the low neutrophil counts reported in these subjects. Subjects either had low counts at baseline or isolated spurious findings that resolved while subjects remained in the study on treatment.

9.6.6 Body Weight

Many antipsychotics are associated with clinically significant weight gain that can profoundly affect medication compliance and the patient's general medical well-being. Therefore the effects of pimavanserin on weight were assessed in the PD psychosis program.

The summary of mean and median change in weight from baseline is presented in Table 9–28. No treatment group experienced mean or median weight gain. Mean and median changes from baseline were similar between pimavanserin and placebo groups. Comparisons between treatment groups and placebo were not statistically significant.

Table 9–28 Summary of Mean Changes from Baseline to Week 6 and 90% CI in Body Weight for Subjects in the PDP6 Population

	Pimavanserin			Placebo
Statistic	8.5 mg (N=140)	17 mg (N=41)	34 mg (N=202)	(N=231)
n	117	35	171	201
Mean (SD)	-0.2 (3.47)	-0.9 (3.13)	0.0 (2.60)	-0.2 (1.32)
Median	0.0	-0.2	0.0	0.0
Min, Max	-17, 24	-18, 1	-19, 18	-5, 3
ANOVA LSM (SE)*	-0.2 (0.22)	-0.9 (0.29)	0.0 (0.15)	-0.2 (0.17)
90% CI	(-0.5, 0.2)	(-1.4, -0.4)	(-0.2, 0.3)	(-0.5, 0.1)
Diff in ANOVA LSM (SE)**	0.1 (0.27)	-0.7 (0.31)	0.2 (0.21)	0.0
90% CI of Diff	(-0.4, 0.5)	(-1.2, -0.2)	(-0.1, 0.6)	0.0

* LSM = Least-squares mean from ANOVA model with treatment as a factor.

** Pairwise difference between least-squared means for PIM and placebo (PIM - Placebo)

Consistent with these results, few subjects in the PDP6 Population experienced clinically significant (≥7%) weight gain (Table 9–29). The 8.5 mg group had the most subjects with ≥7% weight gain. The 17 mg and 34 mg groups had a similar rate of ≥7% weight gain as the placebo group. Thus, no apparent dose response was observed for weight gain. Rates of ≥7% weight loss were higher than ≥7% weight gain. There was more clinically significant weight loss in the pimavanserin groups than in the placebo group. As with weight gain, the 8.5 mg group had the most subjects with ≥7% weight loss. No apparent dose response was observed.

Table 9–29 Incidence of Body Weight Changes ≥7% from Baseline for Subjects in the PDP6 Population

	Number of Subjects (%)				
	Pimavanserin				
Weight Change	8.5 mg (n=131)	17 mg (n=40)	34 mg (n=189)	All-PIM (n=360)	Placebo (n=221)
Weight Increase ≥7%					
N	131	40	189	360	221
Overall Post-baseline	3 (2.3)	0	1 (0.5)	4 (1.1)	1 (0.5)
Weight Decrease ≥7%					
N	131	40	189	360	221
Overall Post-baseline	4 (3.1)	1 (2.5)	5 (2.6)	10 (2.8)	2 (0.9)

In the PDP6 Population, AEs of weight increased were not observed in either treatment group. TEAEs related to weight-loss are shown in Table 9–30. The rates of weight loss events were similar between the All-PIM and placebo groups (1.8% and 1.7%, respectively). The pimavanserin 34 mg group had the lowest rate of weight loss events (0.5%).

Table 9–30 TEAEs of Weight-Loss Related Events by Preferred Term in the PDP6 Population

Special Adverse Event Category Preferred Term	Pimavanserin				Placebo
	8.5 mg (N=140) n (%)	17 mg (N=41) n (%)	34 mg (N=202) n (%)	All-PIM (N=383) n (%)	(N=231) n (%)
Weight-Loss Related Events	**5 (3.6)**	**1 (2.4)**	**1 (0.5)**	**7 (1.8)**	**4 (1.7)**
Decreased appetite	3 (2.1)	1 (2.4)	1 (0.5)	5 (1.3)	3 (1.3)
Weight decreased	3 (2.1)	0	1 (0.5)	4 (1.0)	1 (0.4)
Abnormal loss of weight	0	0	0	0	1 (0.4)

A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30 days.

Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.

Denominators for the percentages were the number of subjects in each treatment group.

To understand weight gain and weight loss in the PDPLT patient population, changes in weight were assessed by body mass index (BMI) subgroups (Table 9–31). Subjects with high BMI at baseline had more frequent clinically significant weight loss (42%) than weight gain (2%) during the study. Subjects with low BMI at baseline had a higher rate of clinically significant weight gain than subjects with high BMI at baseline (25% and 2%, respectively).

Table 9–31 Incidence of Clinically Meaningful Weight Change or Abnormality (Overall Post-baseline Body Weight Changes ≥7% and BMI of <19 or >32 kg/m^2) for Subjects in the PDPLT Population

Category Post-baseline	Criterion at Baseline	PIM 34 mg (N=498)	
		N[a]	Overall Post-baseline n (%)[b]
Weight Decrease ≥7% [c]	All	494	155 (31.4)
	BMI <19	24	6 (25.0)
	BMI 19 to 32	415	126 (30.4)
	BMI >32	50	21 (42.0)
Weight Increase ≥7% [c]	All	494	45 (9.1)
	BMI <19	24	4 (16.7)
	BMI 19 to 32	415	39 (9.4)
	BMI >32	50	1 (2.0)
BMI <19 kg/m^2	All	494	55 (11.1)
	BMI <19	24	22 (91.7)
	BMI 19 to 32	415	33 (8.0)
	BMI >32	50	0
BMI >32 kg/m^2	All	494	56 (11.3)
	BMI <19	24	0
	BMI 19 to 32	415	8 (1.9)
	BMI >32	50	48 (96.0)

[a] Number of subjects with at least 1 clinically meaningful weight change or abnormality within the specified time period.

[b] The denominator for each period was number of subjects who had baseline and at least 1 post-baseline weight measurements within the specified time period.

[c] Weight decrease or increase from baseline (date of first study dose). For weight decrease criterion, if there were multiple assessments for the same time period, the lowest value in that time period was used for analysis. For weight increase criterion if there were multiple assessments for the same time period, the highest value in that time period was used for analysis.

These results suggest that the weight profile of pimavanserin is different than other antipsychotics. Weight gain was not associated with pimavanserin treatment. Subjects experienced a mean weight loss comparable to placebo in the double-blind trials. Clinically significant weight loss was more frequently observed than clinically significant weight gain. Additionally, subjects with high BMI at baseline had higher rates of clinically significant weight loss than did subjects with low BMI at baseline.

9.6.7 Hyperglycemia and Diabetes Mellitus

Hyperglycemia and diabetes mellitus are events associated with many current antipsychotics, and were further evaluated in the PD psychosis program by evaluation of non-fasting glucose levels and assessment of AEs related to diabetes.

In the PDP6 Population, the mean change from baseline on non-fasting glucose was similar across pimavanserin groups and placebo (Table 9–32). Adverse events were also similar between pimavanserin and placebo groups (Table 9–33).

Table 9–32 Glucose: Mean Changes from Baseline to Week 6 for Subjects in the PDP6 Population

Analyte (unit)	Pimavanserin 8.5 mg Mean (SD)	Pimavanserin 17 mg Mean (SD)	Pimavanserin 34 mg Mean (SD)	Pimavanserin All-PIM Mean (SD)	Placebo Mean (SD)
	(N=140)	(N=41)	(N=202)	(N=383)	(N=231)
Glucose Panel (non-fasting)	n=117	n=35	n=168	n=320	n=192
Glucose (mmol/L)	0.05 (1.156)	0.06 (1.754)	0.09 (1.671)	0.07 (1.508)	0.19 (1.694)

Table 9–33 TEAEs of Metabolic-Related Events by Preferred Term in the PDP6 Population

Special Adverse Event Category / Preferred Term	Pimavanserin 8.5 mg (N=140) n (%)	Pimavanserin 17 mg (N=41) n (%)	Pimavanserin 34 mg (N=202) n (%)	Pimavanserin All-PIM (N=383) n (%)	Placebo (N=231) n (%)
Metabolic-Related Events	**1 (0.7)**	**0**	**0**	**1 (0.3)**	**1 (0.4)**
Blood glucose increased	1 (0.7)	0	0	1 (0.3)	0
Hyperglycaemia	0	0	0	0	1 (0.4)

A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30 days.

Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.

Denominators for the percentages were the number of subjects in each treatment group.

In the PDP6 Population, events of increased blood glucose were reported in 1 subject in the pimavanserin 8.5 mg group and hyperglycemia was reported in 1 placebo subject. There were no reports of increased glucose, hyperglycemia or diabetes mellitus in the 17 mg and 34 mg groups. There were no significant risk differences between pimavanserin and placebo for any of these events (or for the overall incidences in this TEAE grouping), and none were serious or led to discontinuation of study drug or the study.

In the PDPLT Population, 7 glucose-related events were reported in the open-label studies. Two events (blood glucose increased and blood glucose decreased) were reported during the first year of the studies; the other 5 events occurred during the next 3 years of the studies. No events were reported in subjects with >4 years exposure. Overall, the event of blood glucose increased was the experienced by 2 subjects (0.4%). Other events (glucose tolerance increased, blood glucose decreased, diabetes mellitus, and hyperglycemia) were each reported once (0.2%).

Overall, data from pimavanserin studies indicate that pimavanserin was not associated with hyperglycemic events.

9.6.8 Infection-Related Adverse Events

Infections are common in the elderly population, including patients with PD. Therefore, rates of infection-related events were assessed in the double-blind studies.

Table 9–34 shows the rates of infection-related events in the PDP6 Population. The 8.5 mg and 17 mg groups had numerically lower rates of infection-related events did the placebo group; the 34 mg group had slightly higher rate compared to placebo. Urinary tract infection (UTI) was the most common event, occurring in multiple subjects during the study, as would be expected in elderly patients.

Respiratory infections (pneumonia, aspiration pneumonia, and bronchitis) also occurred at similar rates between treatment groups.

In summary, controlled study data did not show increase in risk of infection with pimavanserin treatment.

Table 9–34 TEAEs of Infection-Related Events by Preferred Term in the PDP6 Population

Special Adverse Event Category	Pimavanserin				Placebo
	8.5 mg (N=140)	17 mg (N=41)	34 mg (N=202)	All-PIM (N=383)	(N=231)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)
Infection-Related Events	**7 (5.0)**	**1 (2.4)**	**19 (9.4)**	**27 (7.0)**	**17 (7.4)**
Urinary tract infection	5 (3.6)	1 (2.4)	15 (7.4)	21 (5.5)	16 (6.9)
Bronchitis	1 (0.7)	0	2 (1.0)	3 (0.8)	1 (0.4)
Sepsis	1 (0.7)	0	1 (0.5)	2 (0.5)	1 (0.4)
Leukocyturia	0	0	1 (0.5)	1 (0.3)	1 (0.4)
Pneumonia aspiration	0	0	1 (0.5)	1 (0.3)	1 (0.4)
Septic shock	0	0	1 (0.5)	1 (0.3)	0
Pneumonia	0	0	0	0	1 (0.4)
Urosepsis	0	0	0	0	1 (0.4)

A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30 days.

Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.

Denominators for the percentages were the number of subjects in each treatment group.

9.6.9 Sedation

Sedation-related events are associated with the class effects of atypical antipsychotics. Daytime sedation, a prominent side effect, is also associated with increased rates of infection and falls, particularly in the elderly (Ballard and Howard, 2006). Therefore, sedation-related events were assessed in the double-blind studies.

Table 9–35 shows the rates of sedation-related events in the PDP6 Population. Low event rates were observed in this population; the specific term "sedation" was not reported at all. Although the pimavanserin 34 mg group had the numerically highest rates of sedation-related events, events rates were generally similar across treatment groups. There was no apparent dose-response relationship among the pimavanserin groups.

These data suggest that pimavanserin was not associated with sedation. This observation is consistent with the efficacy observation that pimavanserin significantly reduced daytime sleepiness (i.e., improved daytime wakefulness) compared to placebo.

Table 9–35 TEAEs of Sedation-Related Events by Preferred Term: PDP6 Population

	Pimavanserin				Placebo
Special Adverse Event Preferred Term	8.5 mg (N=140)	17 mg (N=41)	34 mg (N=202)	All-PIM (N=383)	(N=231)
	n(%)	n (%)	n (%)	n (%)	n(%)
Sedation-related Events	**8 (5.7)**	**2 (4.9)**	**13 (6.4)**	**23 (6.0)**	**12 (5.2)**
Sedation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	5 (3.6)	1 (2.4)	5 (2.5)	11 (2.9)	6 (2.6)
Fatigue	1 (0.7)	1 (2.4)	5 (2.5)	7 (1.8)	5 (2.2)
Asthenia	0 (0.0)	0 (0.0)	3 (1.5)	3 (0.8)	1 (0.4)
Lethargy	1 (0.7)	0 (0.0)	2 (1.0)	3 (0.8)	0 (0.0)
Hypersomnia	2 (1.4)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)

A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the first administration of study drug and before or on last dose date +30 days.

Subjects may have more than one TEAE per system organ class or preferred term, subjects were counted at most once per system organ class and preferred term.

Denominators for the percentages were the number of subjects in each treatment group.

9.7 Safety Conclusions

The pimavanserin PD psychosis development program is the largest well-controlled safety database in patients with PD psychosis. Overall, more than 1200 people have been exposed to pimavanserin, of whom more than 600 subjects had PD psychosis. Their diagnosis of PD had an average duration of 10 years, and an average 3-year duration of psychosis associated with PD. Serious medical co-morbidities were common, across all system organ classes, as would be expected in elderly patients with a progressive neurodegenerative disorder. Over 450 subjects have received once-daily 34 mg doses, many over an extended period of time. Over 150 subjects had 2 years of pimavanserin treatment; the mean duration of treatment with the pimavanserin 34 mg dose was more than 14 months.

In the 6-week double-blind, placebo-controlled studies, adverse events experienced by subjects treated with pimavanserin were consistent with the subjects' age and medical condition. TEAE rates were generally similar to placebo. No dose response was observed.

Numerically more early discontinuations, SAEs, and deaths were observed in the pimavanserin groups compared to placebo. However, the overall event rates were small; medical review did not find any underlying mechanism and the events were generally reflective of the underlying comorbidities of the population.

Subjects who completed the short-term studies were generally allowed to continue in the long-term study as long as there was a favorable benefit-to-risk assessment, as judged by the investigator, based on the patient's medical need and clinical response. In many cases, subjects remained in the study while medically ill, including hospitalization and hospice care. Mean duration of treatment in the long-term studies was 2.5 years. Adverse events during their participation were consistent with those observed in the 6-week studies and their underlying medical conditions.

In the 6-week studies, a mean 5-8 msec prolongation of the QTc interval was observed. This finding was not associated with AEs in controlled studies, and there were no meaningful outliers observed in a TQT study of pimavanserin. These results were consistent with PK/PD modeling of data from the TQT study, which showed plateauing of prolongation at higher plasma concentrations.

A medical review of events of special interest showed that pimavanserin had a distinct safety and tolerability profile relative to currently used antipsychotics. The rates of orthostatic hypotension and falls were numerically lower than for placebo. Pimavanserin was not associated with weight gain. More subjects experienced clinically significant weight loss than weight gain; weight loss was more prominent in subjects with higher baseline BMI values. Pimavanserin was not associated with liver abnormalities or leukopenia/agranulocytosis. Rates of infection were similar between pimavanserin groups and placebo.

Unlike other antipsychotics, pimavanserin was not associated with motor impairment at therapeutic doses. Pimavanserin treatment met prespecified non-inferiority criteria to placebo. Thus, the efficacy benefits of pimavanserin treatment did not come at the expense of worsening Parkinsonism.

In summary, pimavanserin demonstrated an acceptable safety and tolerability profile that is appropriate for short- and long-term treatment of PD psychosis. Identified safety risks are manageable with the following activities:

- Continual pharmacovigilance postmarketing surveillance, including ongoing medical review for signal detection and evaluation, monthly trend analyses, and appropriate reporting of identified signals

- For events of death, diligent efforts to contact the healthcare provider and gather follow-up information utilizing a structured questionnaire
- Labeling to raise awareness of the risk of QT interval prolongation amongst health professionals and to minimize the risk of serious consequences (syncope, ventricular tachyarrhythmias) in patients who develop QT interval prolongation, including appropriate warning and precautions to avoid the use of pimavanserin in combination with other drugs known to prolong QTc
- Label recommendations to reduce pimavanserin dose by 50% if pimavanserin is co-administered with a moderate or strong CYP3A4 inhibitor

10 Benefit-Risk Summary

Parkinson's disease psychosis is a serious progressive medical condition for which there is no available approved treatment. Over the course of their illness, more than 50 percent of patients with PD will develop psychotic symptoms, with an adverse impact on their quality of life and the course of their disease.

Despite the lack of approved treatment, a substantial number of patients with PD psychosis receive antipsychotic drug therapy. Many of these drugs have not demonstrated efficacy in controlled trials or are known to cause worsening of motor symptoms. Others are rarely used due to safety concerns or extensive monitoring burden.

Left untreated, PD psychosis has severe consequences for patients, families, and caregivers. Psychotic symptoms are the single highest reason for institutionalization among patients with PD, an event that is accompanied by substantial morbidity and mortality.

Pimavanserin provides an alternative approach to the treatment of psychosis in Parkinson's patients with its highly targeted and selective receptor binding profile. This represents a new pharmacologic paradigm, particularly suitable for patients requiring dopaminergic therapy.

Pimavanserin has demonstrated robust efficacy in reducing both hallucinations and delusions in PD psychosis patients without causing dopamine blockade. Phase 3, pivotal Study 020 has provided clinically and statistically persuasive evidence of pimavanserin efficacy in the treatment of psychotic symptoms associated with PD. Pimavanserin 34 mg has demonstrated consistent efficacy across multiple and independent efficacy endpoints, patient subgroups, and sensitivity efficacy analyses. Clinically important and substantial effect size was observed not only on the primary efficacy endpoint, but across all clinical efficacy measures including various responder definitions and including complete responders. Importantly, clinical benefits of pimavanserin are achieved without the negative impact on motor symptoms of PD, and without a number of other safety concerns associated with atypical antipsychotics.

The clinical program for pimavanserin has identified two key clinical risks that require thoughtful consideration.

First, mild to moderate QT prolongation was observed with pimavanserin at the recommended clinical dose. This risk is manageable through appropriate warning and precautions in the Package Insert. Second, metabolism of pimavanserin is significantly affected by strong CYP3A4 inhibitors. Therefore, when prescribed with moderate to strong CYP3A4 inhibitors, a reduction of the pimavanserin dose by 50% is recommended.

There is an observed increase in the reported SAEs for subjects treated with pimavanserin compared to placebo in the 6-week, controlled studies. A complete review of these events did not identify a common underlying mechanism behind this observation.

An imbalance in the number of deaths in the controlled studies was also observed. However, with small numbers of reported events it is difficult to reliably assess whether or not this suggests an association with pimavanserin treatment. A review and medical analysis of the reported deaths indicated that the observed cases were consistent with the risk factors associated with the background disease and medical comorbidities. However, the seriousness of these events requires continued focus and further evaluation through postmarketing pharmacovigilance.

Conclusion

Clinically meaningful benefit with improvements in both hallucinations and delusions, two cardinal symptoms of PD psychosis, were observed in clinical trials with pimavanserin. Robust improvements were observed consistently across multiple measures, subgroups, and range of PD psychosis symptoms without adverse effects on motor function. Pimavanserin demonstrated overall acceptable tolerability with identified safety risks manageable through labeling and pharmacovigilance activities.

The benefits of pimavanserin for patients with PD psychosis clearly outweigh the potential risks, and the product merits approval for the requested indication.

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Appendix A Scale for the Assessment of Positive Symptoms[5]

[5] Andreasen NC: Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, IA, University of Iowa, 1984. Permission to include this publication in the briefing document was granted by the author. Unauthorized reproduction or use of the content of this publication without written consent from the author is prohibited.

SCALE FOR THE ASSESSMENT OF POSITIVE SYMPTOMS

(SAPS)

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(SAS Variable Name edition: 2000)

INTRODUCTION

This scale is designed to assess positive symptoms, principally those that occur in schizophrenia. It is intended to serve as a complementary instrument to the Scale for the Assessment of Negative Symptoms (SANS). These positive symptoms include hallucinations, delusions, bizarre behavior, and positive formal thought disorder.

As in the case of the SANS, the investigator using this instrument will need to decide on an appropriate "time set". The instrument was developed with the exception that, in general, the time set will cover the past month as in the case of SANS. This scale can also be used in psychopharmacologic research in order to make weekly ratings and chart the subject's response to treatment.

Investigators using this instrument, particularly in combination with the SANS, will need to use a standard clinical interview in order to evaluate the subject's symptoms. Since positive formal thought disorder is an important positive symptom, it is recommended that, in doing this interview, the investigator begin talking with the subject on a relatively neutral topic for five to ten minutes in order to observe the subject's manner of speaking and responding. Thereafter, he can begin to ask specific questions about the various positive symptoms. Suggested probes are provided in the interview guide.

In addition to using a clinical interview, the investigator should also draw on other sources of information, such as direct observation, reports from the subject's family, reports from nurses, and reports from the subject himself. In general, the subject can usually be considered a relatively reliable informant concerning delusions and hallucinations if he is able to communicate clearly and will comply with a clinical interview. On the other hand, the interviewer will usually have to rely on observation and reports from outside sources in order to evaluate bizarre behavior and positive formal thought disorder.

The last item describing each major type of positive symptom is an overall global rating. This should be a true global rating based on taking into account both the nature and the severity of the various types of symptoms observed. In some cases, a single symptom (e.g., extremely severe persecutory delusions) may lead to a very high global rating, even if other symptoms of this type are not present.

HALLUCINATIONS

Hallucinations represent an abnormality in perception. They are false perceptions occurring in the absence of some identifiable external stimulus. They may be experienced in any of the sensory modalities, including hearing, touch, taste, smell, and vision. True hallucinations should be distinguished from illusions (which involve a misperception of an external stimulus), hypnogogic and hypnopompic experiences (which occur when the subject is falling asleep or waking up), or normal thought processes that are exceptionally vivid. If the hallucinations have a religious quality, then they should be judged within the context of what is normal for the subject's social and cultural background. Hallucinations occurring under the immediate influence of alcohol, drugs, or serious physical illness should not be rated as present. The subject should always be requested to describe the hallucination in detail.

Auditory Hallucinations

The subject has reported voices, noises, or sounds. The commonest auditory hallucinations involve hearing voices speaking to the subject or calling him names. The voices may be male or female, familiar or unfamiliar, and critical or complimentary. Typically, subjects suffering from schizophrenia experience the voices as unpleasant and negative. Hallucinations involving sounds rather than voices, such as noises or music, should be considered less characteristic and less severe.

Have you ever heard voices or other sounds when no one is around?

What did they say?

None	0	SS36
Questionable	1	
Mild: Subject hears noises or single words; they occur only occasionally	2	
Moderate: Clear evidence of voices; they have occurred at least weekly	3	
Marked: Clear evidence of voices which occur almost every day	4	
Severe: Voices occur often every day	5	

Voices Commenting

Voices commenting are a particular type of auditory hallucination which phenomenologists as Kurt Schneider consider to be pathognomonic of schizophrenia, although some recent evidence contradicts this. These hallucinations involve hearing a voice that makes a running commentary on the subject's behavior or thought as it occurs. If this is the only type of auditory hallucination that the subject hears, it should be scored instead of auditory hallucinations (No. 1 above). Usually, however, voices commenting will occur in addition to other types of auditory hallucinations.

Have you ever heard voices commenting on what you are thinking or doing?

What do they say?

None	0	SS37
Questionable	1	
Mild: Subject hears noises or single words; they occur only occasionally	2	
Moderate: Clear evidence of voices; they have occurred at least weekly	3	
Marked: Clear evidence of voices which occur almost every day	4	
Severe: Voices occur often every day	5	

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Voices Conversing

Like voices commenting, voices conversing are considered a Schneiderian first-rank symptom. They involve hearing two or more voices talking with one another, usually discussing something about the subject. As in the case of voices commenting, they should be scored independently of other auditory hallucinations.

Have you heard two or more voices talking with each other?

What did they say?

None	0	SS38
Questionable	1	
Mild: Subject hears noises or single words; they occur only occasionally	2	
Moderate: Clear evidence of voices; they have occurred at least weekly	3	
Marked: Clear evidence of voices which occur almost every day	4	
Severe: Voices occur often every day	5	

Somatic or Tactile Hallucinations

These hallucinations involve experiencing peculiar physical sensations in the body. They include burning sensations, tingling, and perceptions that the body has changed in shape or size.

Have you ever had burning sensations or other strange feelings in your body?

What were they?

Did your body ever appear to change in shape or size?

None	0	SS39
Questionable	1	
Mild: Subject experiences peculiar physical sensations; they occur only occasionally	2	
Moderate: Clear evidence of somatic or tactile hallucinations; they have occurred at least weekly	3	
Marked: Clear evidence of somatic or tactile hallucinations which occur almost every day	4	
Severe: Hallucinations occur often every day	5	

Olfactory Hallucinations

The subject experiences unusual smells which are typically quite unpleasant. Sometimes the subject may believe that he himself smells. This belief should be scored here if the subject can actually smell the odor himself, but should be scored among delusions if he only believes that others can smell the odor.

Have you ever experienced any unusual smells or smells that others do not notice?

What were they?

None	0	SS40
Questionable	1	
Mild: Subject experiences unusual smells; they occur only occasionally	2	
Moderate: Clear evidence of olfactory hallucinations; they have occurred at least weekly	3	
Marked: Clear evidence of olfactory hallucinations; they occur almost every day	4	
Severe: Olfactory hallucinations occur often every day	5	

Visual Hallucinations

The subject sees shapes or people that are not actually present. Sometimes these are shapes or colors, but most typically they are figures of people or human-like objects. They may also be characters of a religious nature, such as the Devil or Christ. As always, visual hallucinations involving religious themes should be judged within the context of the subject's cultural background. Hypnogogic and hypnopompic visual hallucinations (which are relatively common) should be excluded, as should visual hallucinations occurring when the subject has been taking hallucinogenic drugs.

Have you had visions or seen things that other people cannot?

What did you see?

Did this occur when you were falling asleep or waking up?

None	0	SS41
Questionable	1	
Mild: Subject experiences visual hallucinations; they occur only occasionally	2	
Moderate: Clear evidence of visual hallucinations; they have occurred at least weekly	3	
Marked: Clear evidence of visual hallucinations which occur almost every day	4	
Severe: Hallucinations occur often every day	5	

Global Rating of Severity of Hallucinations

This global rating should be based on the duration and severity of hallucinations, the extent of the subject's preoccupation with the hallucinations, his degree of conviction, and their effect on his actions. Also consider the extent to which the hallucinations might be considered bizarre or unusual. Hallucinations not mentioned above, such as those involving taste, should be included in this rating.

None	0	SS42
Questionable	1	
Mild: Hallucinations definitely present, but occur infrequently; at times the subject may question their existence	2	
Moderate: Hallucinations are vivid and occur occasionally; they may bother him to some extent	3	
Marked: Hallucinations are quite vivid, occur frequently, and pervade his life	4	
Severe: Hallucinations occur almost daily and are sometimes unusual or bizarre; they are very vivid and extremely troubling	5	

DELUSIONS

Delusions represent an abnormality in content of thought. They are false beliefs that cannot be explained on the basis of the subject's cultural background. Although delusions are sometimes defined as "fixed false beliefs," in their mildest form delusions may persist only for weeks to months, and the subject may question his beliefs or doubt them. The subject's behavior may or may not be influenced by his delusions. The rating of severity of individual delusions and of the global severity of delusional thinking should take into account their persistence, their complexity, the extent to which the subject acts on them, the extent to which the subject doubts them, and the extent to which the beliefs deviate from those that normal people might have. For each positive rating, specific examples should be noted in the margin.

Persecutory Delusions

People suffering from persecutory delusions believe that they are being conspired against or persecuted in some way. Common manifestations include the belief that one is being followed, that one's mail is being opened, that one's room or office is bugged, that the telephone is tapped, or that police, government officials, neighbors, or fellow workers are harassing the subject. Persecutory delusions are sometimes relatively isolated or fragmented, but sometimes the subject has a complex set of delusions involving both a wide range of forms of persecution and a belief that there is a well-designed conspiracy behind them. For example, a subject may believe that his house is bugged and that he is being followed because the government wrongly considers him a secret agent for a foreign government; this delusion may be so complex that it explains almost everything that happens to him. The ratings of severity should be based on duration and complexity.

Have people been bothering you in any way?

Have you felt that people are against you?

Has anyone been trying to harm you in any way?

Has anyone been watching or monitoring you?

None	0 SS43
Questionable	1
Mild: Delusional beliefs are simple and may be of several different types; subject may question them occasionally	2
Moderate: Clear, consistent delusion that is firmly held	3
Marked: Consistent, firmly-held delusion that the subject acts on	4
Severe: Complex well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre	5

Delusions of Jealousy

The subject believes that his/her mate is having an affair with someone. Miscellaneous bits of information are construed as "evidence". The person usually goes to great effort to prove the existence of the affair, searching for hair in the bedclothes, the odor of shaving lotion or smoke on clothing, or receipts or checks indicating a gift has been bought for the lover. Elaborate plans are often made in order to trap the two together.

Have you ever worried that your husband (wife) might be unfaithful to you?

What evidence do you have?

None	0 SS44
Questionable	1
Mild: Delusion clearly present, but the subject may question it occasionally	2
Moderate: Clear consistent delusion that is firmly held	3
Marked: Consistent, firmly-held delusion that the subject acts on	4
Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre	5

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Delusions of Sin or Guilt

The subject believes that he has committed some terrible sin or done something unforgivable. Sometimes the subject is excessively or inappropriately preoccupied with things he did wrong as a child, such as masturbating. Sometimes the subject feels responsible for causing some disastrous event, such as a fire or accident, with which he in fact has no connection. Sometimes these delusions may have a religious flavor, involving the belief that the sin is unpardonable and that the subject will suffer eternal punishment from God. Sometimes the subject simply believes that he deserves punishment by society. The subject may spend a good deal of time confessing these sins to whomever will listen.

Have you ever felt that you have done some terrible thing that you deserve to be punished for?

None	0 SS45
Questionable	1
Mild: Delusional beliefs may be simple and may be of several different types; subject may question them occasionally	2
Moderate: Clear, consistent delusion that is firmly held	3
Marked: Consistent, firmly-held delusion that the subject acts on	4
Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre	5

Grandiose Delusions

The subject believes that he has special powers or abilities. He may think he is actually some famous personage, such as a rock star, Napoleon, or Christ. He may believe he is writing some definitive book, composing a great piece of music, or developing some wonderful new invention. The subject is often suspicious that someone is trying to steal his ideas, and he may become quite irritable if his ideas are doubted.

Do you have any special or unusual abilities or talents?

Do you feel you are going to achieve great things?

None	0 SS46
Questionable	1
Mild: Delusional beliefs may be simple and may be of several different types; subject may question them occasionally	2
Moderate: Clear, consistent delusion that is firmly held	3
Marked: Consistent, firmly-held delusion that the subject acts on	4
Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre	5

Religious Delusions

The subject is preoccupied with false beliefs of a religious nature. Sometimes these exist within the context of a conventional religious system, such as beliefs about the Second Coming, the Antichrist, or possession by the Devil. At other times, they may involve an entirely new religious system or a pastiche of beliefs from a variety of religions, particularly Eastern religions, such as ideas about reincarnation or Nirvana. Religious delusions may be combined with grandiose delusions (if the subject considers himself a religious leader), delusions of guilt, or delusions of being controlled. Religious delusions must be outside the range considered normal for the subject's cultural and religious background.

Are you a religious person?

Have you had any unusual religious experiences?

What was your religious training as a child?

None	0 SS47
Questionable	1
Mild: Delusional beliefs may be simple and may be of several different types; subject may question them occasionally	2
Moderate: Clear, consistent delusion that is firmly held	3
Marked: Consistent, firmly-held delusion that the subject acts on	4
Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre	5

Somatic Delusions

The subject believes that somehow his body is diseased, abnormal, or changed. For example, he may believe that his stomach or brain is rotting, that his hands or penis have become enlarged, or that his facial features are unusual (dysmorphophobia). Sometimes somatic delusions are accompanied by tactile or other hallucinations, and when this occurs, both should be rated. (For example, the subject believes that he has ballbearings rolling around in his head, placed there by a dentist who filled his teeth, and can actually hear them clanking against one another.)

Is there anything wrong with your body?

Have you noticed any change in your appearance?

None	0 SS48
Questionable	1
Mild: Delusional beliefs may be simple and may be of several different types; subject may question them occasionally	2
Moderate: Clear, consistent delusion that is firmly held	3
Marked: Consistent, firmly-held delusion that the subject acts on	4
Severe: Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre	5

Ideas and Delusions of Reference

The subject believes that insignificant remarks, statements, or events refer to him or have some special meaning for him. For example, the subject walks into a room, sees people laughing, and suspects that they were just talking about him and laughing at him. Sometimes items read in the paper, heard on the radio, or seen on television are considered to be special messages to the subject. In the case of ideas of reference, the subject is suspicious, but recognizes his idea is erroneous. When the subject actually believes that the statements or events refer to him, then this is considered a delusion of reference.

Have you ever walked into a room and thought people were talking about you or laughing at you?

Have you seen things in magazines or on TV that seem to refer to you or contain a special message for you?

Have people communicated with you in any unusual ways?

None	0	SS49
Questionable	1	
Mild: Occasional ideas of reference	2	
Moderate: Have occurred at least weekly	3	
Marked: Occurs at least two to four times weekly	4	
Severe: Occurs frequently	5	

Delusions of Being Controlled

The subject has a subjective experience that his feelings or actions are controlled by some outside force. The central requirement for this type of delusion is an actual strong subjective experience of being controlled. It does not include simple beliefs or ideas, such as that the subject is acting as an agent of God or that friends or parents are trying to coerce him to do something. Rather, the subject must describe, for example, that his body has been occupied by some alien force that is making it move in peculiar ways, or that messages are being sent to his brain by radio waves and causing him to experience particular feelings that he recognizes are not his own.

Have you ever felt you were being controlled by some outside force?

None	0	SS50
Questionable	1	
Mild: Subject has experienced being controlled, but doubts it occasionally	2	
Moderate: Clear experience of control, which has occurred on two or three occasions in a week	3	
Marked: Clear experience of control, which occurs frequently; behavior may be affected	4	
Severe: Clear experience of control which occurs frequently, pervades the subject's life, and often affects his behavior	5	

Delusions of Mind Reading

The subject believes that people can read his mind or know his thoughts. This is different than thought broadcasting (see below) in that it is a belief without a percept. That is, the subject subjectively experiences and recognizes that others know his thoughts, but he does not think that they can be heard out loud.

Have you ever had the feeling that people could read your mind?

None	0	SS51
Questionable	1	
Mild: Subject has experienced mind reading, but doubts it occasionally	2	
Moderate: Clear experience of mind reading which has occurred on two or three occasions in a week	3	
Marked: Clear experience of mind reading which occurs frequently; behavior may be affected	4	
Severe: Clear experience of mind reading which occurs frequently, pervades the subject's life, and often affects his behavior	5	

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Thought Broadcasting

The subject believes that his thoughts are broadcast so that he or others can hear them. Sometimes the subject experiences his thoughts as a voice outside his head; this is an auditory hallucination as well as a delusion. Sometimes the subject feels his thoughts are being broadcast although he cannot hear them himself. Sometimes he believes that his thoughts are picked up by a microphone and broadcast on the radio or television.

Have you ever heard your own thoughts out loud, as if they were a voice outside your head?

Have you ever felt your thoughts were broadcast so other people could hear them?

None	0 SS52
Questionable	1
Mild: Subject has experienced thought broadcasting, but doubts it occasionally	2
Moderate: Clear experience of thought broadcasting which has occurred on two or three occasions in a week	3
Marked: Clear experience of thought broadcasting which occurs frequently; behavior may be affected	4
Severe: Clear experience of thought broadcasting which occurs frequently, pervades the subject's life, and often affects his behavior	5

Thought Insertion

The subject believes that thoughts that are not his own have been inserted into his mind. For example, the subject may believe that a neighbor is practicing voodoo and planting alien sexual thoughts in his mind. This symptom should not be confused with experiencing unpleasant thoughts that the subject recognizes as his own, such as delusions of persecution or guilt.

Have you ever felt that thoughts were being put into your head by some outside force?

Have you ever experienced thoughts that didn't seem to be your own?

None	0 SS53
Questionable	1
Mild: Subject has experienced thought insertion, but doubts it occasionally	2
Moderate: Clear experience of thought insertion which has occurred on two or three occasions in a week	3
Marked: Clear experience of thought insertion which occurs frequently; behavior may be affected	4
Severe: Thought insertion which occurs frequently, pervades the subject's life and affects behavior	5

Thought Withdrawal

The subject believes that thoughts have been taken away from his mind. He is able to describe a subjective experience of beginning a thought and then suddenly having it removed by some outside force. This symptom does not include the mere subjective recognition of alogia.

Have you ever felt your thoughts were taken away by some outside force?

None	0	SS54
Questionable	1	
Mild: Subject has experienced thought withdrawal, but doubts it occasionally	2	
Moderate: Clear experience of thought withdrawal which has occurred on two or three occasions in a week	3	
Marked: Clear experience of thought withdrawal which occurs frequently; behavior may be affected	4	
Severe: Clear experience of thought withdrawal which occurs frequently, pervades the subject's life and often affects his behavior	5	

Global Rating of Severity of Delusions

The global rating should be based on duration and persistence of delusions, the extent of the subject's preoccupation with the delusions, his degree of conviction, and their effect on his actions. Also consider the extent to which the delusions might be considered bizarre or unusual. Delusions not mentioned above should be included in this rating.

None	0	SS55
Questionable	1	
Mild: Delusion definitely present but, at times, the subject questions the belief	2	
Moderate: The subject is convinced of the belief, but it may occur infrequently and have little effect on his behavior	3	
Marked: The delusion is firmly held; it occurs frequently and affects the subject's behavior	4	
Severe: Delusions are complex, well-formed, and pervasive; they are firmly held and have a major effect on the subject's behavior; they may be somewhat bizarre or unusual	5	

BIZARRE BEHAVIOR

The subject's behavior is unusual, bizarre, or fantastic. For example, the subject may urinate in a sugar bowl, paint the two halves of his body different colors, or kill a litter of pigs by smashing their heads against a wall. The information for this item will sometimes come from the subject, sometimes from other sources, and sometimes from direct observation. Bizarre behavior due to the immediate effects of alcohol or drugs should be excluded. As always, social and cultural norms must be considered in making the ratings, and detailed examples should be elicited and noted.

Clothing and Appearance

The subject dresses in an unusual manner or does other strange things to alter his appearance. For example, he may shave off all his hair or paint parts of his body different colors. His clothing may be quite unusual; for example, he may choose to wear some outfit that appears generally inappropriate and unacceptable, such as a baseball cap backwards with rubber galoshes and long underwear covered by denim overalls. He may dress in a fantastic costume representing some historical personage or a man from outer space. He may wear clothing completely inappropriate to the climatic conditions, such as heavy wools in the midst of summer.

Has anyone made comments about your appearance?

None	0	SS56
Questionable	1	
Mild: Occasional oddities of dress or appearance	2	
Moderate: Appearance or apparel are clearly unusual and would attract attention	3	
Marked: Appearance or apparel are markedly odd	4	
Severe: Subject's appearance or apparel are very fantastic or bizarre	5	

Social and Sexual Behavior

The subject may do things that are considered inappropriate according to usual social norms. For example, he may masturbate in public, urinate or defecate in inappropriate receptacles, or exhibit his sex organs inappropriately. He may walk along the street muttering to himself, or he may begin talking to people whom he has never met about his personal life (as when riding on a subway or standing in some public place). He may drop to his knees praying and shouting in the midst of a crowd of people, or he may suddenly sit in a yoga position while in the midst of a crowd. He may make inappropriate sexual overtures or remarks to strangers.

Have you ever done anything that others might thing unusual or that has called attention to yourself?

None	0	SS57
Questionable	1	
Mild: Occasional instances of somewhat peculiar behavior	2	
Moderate: Frequent instances of odd behavior	3	
Marked: Very odd behavior	4	
Severe: Extremely odd behavior which may have a fantastic quality	5	

Aggressive and Agitated Behavior

The subject may behave in an aggressive, agitated manner, often quite unpredictably. He may start arguments inappropriately with friends or members of his family, or he may accost strangers on the street and begin haranguing them angrily. He may write letters of a threatening or angry nature to government officials or others with whom he has some quarrel. Occasionally, subjects may perform violent acts such as injuring or tormenting animals, or attempting to injure or kill human beings.

Have you ever done anything to try to harm animals or people?

Have you felt angry with anyone?

How did you express your anger?

None	0 SS58
Questionable	1
Mild: Occasional instances	2
Moderate: For example, writing angry letters to strangers	3
Marked: For example, threatening people, public harangues	4
Severe: For example, mutilating animals, attacking people	5

Repetitive or Stereotyped Behavior

The subject may develop a set of repetitive actions or rituals that he must perform over and over. Frequently, he will attribute some symbolic significance to these actions and believe that they are either influencing others or preventing himself from being influenced. For example, he may eat jelly beans every night for dessert, assuming that different consequences will occur depending on the color of the jelly beans. He may have to eat foods in a particular order, wear particular clothes, or put them on in a certain order. He may have to write messages to himself or to others over and over; sometimes this will be in an unusual or occult language.

Are there any things that you feel you have to do?

None	0 SS59
Questionable	1
Mild: Occasional instances of ritualistic or stereotyped behavior	2
Moderate: For example, eating or dressing rituals lacking symbolic significance	3
Marked: For example, eating or dressing rituals with a symbolic significance	4
Severe: For example, keeping a diary in an incomprehensible language	5

Global Rating of Severity of Bizarre Behavior

In making this rating, the interviewer should consider the type of behavior, the extent to which it deviates from social norms, the subject's awareness of the degree to which the behavior is deviant, and the extent to which it is obviously bizarre.

None	0 SS60
Questionable	1
Mild: Occasional instances of unusual or apparently idiosyncratic behavior; subject usually has some insight	2
Moderate: Behavior which is clearly deviant from social norms and seems somewhat bizarre; subject may have some insight	3
Marked: Behavior which is markedly deviant from social norms and clearly bizarre; subject may have some insight	4
Severe: Behavior which is extremely bizarre or fantastic; may include a single extreme act, e.g., attempting murder; subject usually lacks insight.	5

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POSITIVE FORMAL THOUGHT DISORDER

Positive formal thought disorder is fluent speech that tends to communicate poorly for a variety of reasons. The subject tends to skip from topic to topic without warning, to be distracted by events in the nearby environment, to join words together because they are semantically or phonologically alike even though they make no sense, or to ignore the question asked and ask another. This type of speech may be rapid, and it frequently seems quite disjointed. It has sometimes been referred to as "loose associations." Unlike alogia (negative formal thought disorder), a wealth of detail is provided, and the flow of speech tends to have an energetic, rather than an apathetic, quality to it.

In order to evaluate thought disorder, the subject should be permitted to talk at length on some topic, particularly a topic unrelated to his psychopathology, for as long as five to ten minutes. The interviewer should observe closely the extent to which his sequencing of ideas is well connected. In addition, the interviewer should insist that he clarify or elaborate further if the ideas seem vague or incomprehensible. He should also pay close attention to how well the subject can reply to a variety of different types of questions, ranging from simple (Where were you born?) to more complicated (How do you think the present government is doing?)

The anchor points for these ratings assume that the subject has been interviewed for a total of approximately forty-five minutes. If the interview is shorter, the ratings should be adjusted accordingly.

Derailment (Loose Associations)

A pattern of spontaneous speech in which the ideas slip off one track onto another which is clearly but obliquely related, or onto one which is completely unrelated. Things may be said in juxaposition which lack a meaningful relationship, or the subject may shift idiosyncratically from one frame of reference to another. At times there may be a vague connection between the ideas, and at others none will be apparent. This pattern of speech is often characterized as sounding "disjointed." Perhaps the commonest manifestation of this disorder is a slow, steady slippage, with no single derailment being particularly severe, so that the speaker gets farther and farther off the track with each derailment without showing any awareness that his reply no longer has any connection with the question which was asked. This abnormality is often characterized by lack of cohesion between clauses and sentences and by unclear pronoun references.

Example**:** Interviewer: "Did you enjoy college?" Subject: "Um-hum. Oh hey well, I oh, I really enjoyed some communities I tried it, and the, and the next day when I'd be going out, you know, um, I took control like uh, I put, um, bleach on my hair in, in California. My roommate was from Chicago, and she was going to the junior college. And we lived in the Y.M.C.A., so she wanted to put it, um, peroxide on my hair, and she did, and I got up and looked at the mirror and tears came to my eyes. Now do you understand it, I was fully aware of what was going on but why couldn't I, I . . . why, why the tears? I can't understand that, can you?"

None	0 SS61
Questionable	1
Mild: Occasional instances of derailment, with only slight topic shifts	2
Moderate: Several instances of derailment; subject is sometimes difficult to follow	3
Marked: Frequent instances of derailment; subject is often difficult to follow	4
Severe: Derailment so frequent and/or extreme that the subject's speech is almost incomprehensible	5

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Tangentiality

Replying to a question in an oblique, tangential or even irrelevant manner. The reply may be related to the question in some distant way. Or the reply may be unrelated and seem totally irrelevant. In the past tangentiality has sometimes been used as roughly equivalent to loose associations or derailment. The concept of tangentiality has been partially redefined so that it refers only to answers to questions and not to transitions in spontaneous speech.

Example: Interviewer: "What city are you from?" Subject: "That's a hard question to answer because my parents . . . I was born in Iowa, but I know that I'm white instead of black, so apparently I came from the North somewhere and I don't know where, you know, I really don't know whether I'm Irish or Scandinavian or I don't, I don't believe I'm Polish but I think I'm, I think I might be German or Welsh.

None	0 SS62
Questionable	1
Mild: One or two oblique replies	2
Moderate: Occasional oblique replies (three to four times)	3
Marked: Frequent oblique replies (more than four times	4
Severe: Tangentiality so severe that interviewing the subject is extremely difficult	5

Incoherence (Word Salad, Schizophasia)
A pattern of speech which is essentially incomprehensible at times. Incoherence is often accompanied by derailment. It differs from derailment in that in incoherence the abnormality occurs within the level of the sentence or clause, which contains words or phrases that are joined incoherently. The abnormality in derailment involves unclear or confusing connections between larger units, such as sentences or clauses.

This type of language disorder is relatively rare. When it occurs, it tends to be severe or extreme, and mild forms are quite uncommon. It may sound quite similar to Wernicke's aphasia or jargon aphasia, and in these cases the disorder should only be called incoherence when history and laboratory data exclude the possibility of a past stroke, and formal testing for aphasia is negative.

Exclusions: Mildly ungrammatical constructions or idiomatic usages characteristic of particular regional or ethnic backgrounds, lack of education, or low intelligence.

Example: Interviewer: "What do you think about current political issues like the energy crisis?" Subject: "They're destroying too many cattle and oil just to make soap. If we need soap when you can jump into a pool of water, and then when you go to buy your gasoline, my folks always thought they should, get pop but the best thing to get, is motor oil, and, money. May, may as well go there and, trade in some, pop caps and, uh, tires, and tractors to group, car garages, so they can pull cars away from wrecks, is what I believed in."

None	0 SS63
Questionable	1
Mild: Occasional instances of incoherence	2
Moderate: Frequent bursts of incoherence	3
Marked: At least half of the subject's speech is incomprehensible	4
Severe: Almost all of the subject's speech is incomprehensible	5

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Illogicality

A pattern of speech in which conclusions are reached which do not follow logically. This may take the form of non-sequiturs (= it does not follow), in which the subject makes a logical inference between two clauses which is unwarranted or illogical. It may take the form of faulty inductive inferences. It may also take the form of reaching conclusions based on faulty premises without any actual delusional thinking.

Exclusions: Illogicality may either lead to or result from delusional beliefs. When illogical thinking occurs within the context of a delusional system, it should be subsumed under the concept of delusions and not considered a separate phenomenon representing a different type of thinking disorder. Illogical thinking which is clearly due to cultural or religious values or to intellectual deficit should also be excluded.

Example: "Parents are the people that raise you. Any thing that raises you can be a parent. Parents can be anything -- material, vegetable, or mineral -- that has taught you something. Parents would be the world of things that are alive, that are there. Rocks -- a person can look at a rock and learn something from it, so that would be a parent."

None	0	SS64
Questionable	1	
Mild: Occasional instances of illogicality	2	
Moderate: Frequent instances of illogicality (three or four times)	3	
Marked: Much of the subject's speech is illogical (more than four times)	4	
Severe: Most of the subject's speech is illogical	5	

Circumstantiality

A pattern of speech which is very indirect and delayed in reaching its goal idea. In the process of explaining something, the speaker brings in many tedious details and sometimes makes parenthetical remarks. Circumstantial replies or statements may last for many minutes if the speaker is not interrupted and urged to get to the point. Interviewers will often recognize circumstantiality on the basis of needing to interrupt the speaker in order to complete the process of history-taking within an allotted time. When not called circumstantial, these people are often referred to as "long-winded."

Exclusions: Although it may coexist with instances of poverty of content of speech or loss of goal, it differs from poverty of content of speech in containing excessive amplifying or illustrative detail and from loss of goal in that the goal is eventually reached if the person is allowed to talk long enough. It differs from derailment in that the details presented are closely related to some particular goal or idea and that the particular goal or idea must be, by definition, eventually reached.

None	0	SS65
Questionable	1	
Mild: Occasional instances of circumstantiality	2	
Moderate: Frequent instances of circumstantiality	3	
Marked: At least half of subject's speech is circumstantial	4	
Severe: Most of the subject's speech is circumstantial	5	

Pressure of Speech

An increase in the amount of spontaneous speech as compared to what is considered ordinary or socially customary. The subject talks rapidly and is difficult to interrupt. Some sentences may be left uncompleted because of eagerness to get on to a new idea. Simple questions which could be answered in only a few words or sentences are answered at great length so that the answer takes minutes rather than seconds and indeed may not stop at all if the speaker is not interrupted. Even when interrupted, the speaker often continues to talk. Speech tends to be loud and emphatic. Sometimes speakers with severe pressure will talk without any social stimulation and talk even though no one is listening. When subjects are receiving phenothiazines or lithium, their speech is often slowed down by medication, and then it can be judged only on the basis of amount, volume, and social appropriateness. If a quantitative measure is applied to the rate of speech, then a rate greater than 150 words per minute is usually considered rapid or pressured. This disorder may be accompanied by derailment, tangentiality, or incoherence, but it is distinct from them.

None	0	SS66
Questionable	1	
Mild: Slight pressure of speech; some slight increase in amount, speed, or loudness of speech	2	
Moderate: Usually takes several minutes to answer simple questions, may talk when no one is listening, and/or speaks loudly and rapidly	3	
Marked: Frequently talks as much as three minutes to answer simple questions; sometimes begins talking without social stimulation; difficult to interrupt	4	
Severe: Subject talks almost continually, cannot be interrupted at all, and/or may shout to drown out the speech of others	5	

Distractible Speech

During the course of a discussion or interview, the subject stops talking in the middle of a sentence or idea and changes the subject in response to a nearby stimulus, such as an object on a desk, the interviewer's clothing or appearance, etc.

Example: "Then I left San Francisco and moved to . . . where did you get that tie? It looks like it's left over from the 50's. I like the warm weather in San Diego. Is that a conch shell on your desk? Have you ever gone scuba diving?

None	0	SS67
Questionable	1	
Mild: Is distracted once during an interview	2	
Moderate: Is distracted from two to four times during an interview	3	
Marked: Is distracted from five to ten times during an interview	4	
Severe: Is distracted more than ten times during an interview	5	

Clanging

A pattern of speech in which sounds rather than meaningful relationships apear to govern word choice, so that the intelligibility of the speech is impaired and redundant words are introduced. In addition to rhyming relationships, this pattern of speech may also include punning associations, so that a word similar in sound brings in a new thought.

Example: I'm not trying to make a noise. I'm trying to make sense. If you can make sense out of nonsense, well, have fun. I'm trying to make sense out of sense. I'm not making sense (cents) anymore. I have to make dollars."

None	0	SS68
Questionable	1	
Mild: Occurs once during an interview	2	
Moderate: Occurs from two to four times during an interview	3	
Marked: Occurs five to ten times during an interview	4	
Severe: Occurs more than ten times, or so frequently that the interview is incomprehensible.		

Global Rating of Positive Formal Thought Disorder

In making this rating, the interviewer should consider the type of abnormality, the degree to which it affects the subject's ability to communicate, the frequency with which abnormal speech occurs, and its degree of severity.

None	0	SS69
Questionable	1	
Mild: Occasional instances of disorder; subject's speech is understandable	2	
Moderate: Frequent instances of disorder; subject is sometimes hard to understand	3	
Marked: Subject is often difficult to understand	4	
Severe: Subject is incomprehensible	5	

Appendix B End-of-Text Tables and Figures

Appendix B, Table 1 Summary of Individual Clinical Studies (Completed and Ongoing) with Pimavanserin

Study Suffix (ACP-103-XXX)	Phase	Population	N (n) Randomized (exposed to PIM)	Purpose	Pimavanserin Doses (Unless otherwise specified)	Complete[a], Ongoing or Planned	ACADIA Sponsored?
Pharmacokinetic (PK) Studies							
Healthy Subject PK and Initial Tolerability Study Reports							
001	1	Healthy Subjects	33 (28)	Single-dose safety, tolerability, and PK	17, 43, 85, or 255 mg PIM or placebo (single dose)	Complete (Oct 2003)	Yes[b]
002	1	Healthy Subjects	24 (18)	Multi-dose safety, tolerability, and PK	43, 85, or 128 mg PIM or placebo (QD for 14 days)	Complete (Jun 2003)	Yes[b]
016	1	Healthy Subjects	6 (6)	Single-dose ADME and mass balance	34 mg PIM and 100 µCi of radioactivity (single dose)	Complete (Jul 2007)	Yes
017	1	Healthy Subjects	22 (16)	Multi-dose safety, tolerability and PK	102 or 136 mg PIM or placebo (QD for 7 days)	Complete (Aug 2007)	Yes
Subject PK and Initial Tolerability Study Reports							
005	1b/2a	PD	12 (8)	Multi-dose safety, tolerability and PK	21 or 85 mg PIM or placebo (QD for 14 days)	Complete (Feb 2004)	Yes
PK Studies – Extrinsic Factors							
023	1	Healthy Subjects	20 (20)	Effects of a potent CYP3A blocker (ketoconazole) on PIM PK	34 mg PIM (2-period single dose); 400 mg ketoconazole (QD for 14 days)	Complete (May 2013)	Yes
024	1	Healthy Subjects	20 (20)	Effects of PIM on carbidopa/levodopa PK in subjects receiving concomitant Sinemet®	Sinemet 25-100 IR TID for 3 days (Study Days 1-3); PIM 34 mg QD for 14 days (Study Days 4-17); Sinemet 25-100 IR TID for 3 additional days (Study Days 15-17)	Complete (Jul 2013)	Yes
027	1	Healthy Subjects	24 (24)	Effects of PIM on the PK of midazolam, an accepted probe drug for CYP3A4	Midazolam Syrup 2 mg on Days 1 and 15 (single dose); PIM 34 mg QD on Days 3-14	Complete (Jun 2014)	Yes
029	1	Healthy Subjects	24 (24)	Effects of pimavanserin and AC-279 on the PK of midazolam (an accepted probe drug for CYP3A4) and its metabolites	Midazolam Syrup (2 mg) on Days 1, 3, 20, and 40 (single dose); PIM 34 mg QD on Days 3-40	Complete (Oct 2014)	Yes

Abbreviations and footnotes at end of table.

Appendix B, Table 1 Summary of Individual Clinical Studies (Completed and Ongoing) with Pimavanserin (Continued)

Study Suffix (ACP-103-XXX)	Phase	Population	N (n) Randomized (exposed to PIM)	Purpose	Pimavanserin Tartrate Doses (Unless otherwise specified)	Complete[a], Ongoing or Planned	ACADIA Sponsored?
Pharmacokinetic Studies – Special Populations							
025	1	Subjects with hepatic impairment[c]; Healthy Subjects	48 planned Cohorts of 8, 8, 8, and 24	Effects of hepatic impairment on the PK profile of pimavanserin and AC-279	17 mg PIM (single dose)	Ongoing (Oct 2015)	Yes
026	1	Subjects with renal impairment[d]; Healthy Subjects	24 planned Cohorts of 6, 6, and 12	Effects of renal impairment on the PK profile and safety of pimavanserin and AC-279	34 mg PIM (single dose)	Ongoing (Oct 2015)	Yes
Pharmacodynamic (PD) Studies							
Healthy Subject PD and PK/PD Study Reports							
003	1	Healthy Subjects	4 (4)	Single dose PET	0.85, 1.7, 4.3, 8.5, 17, or 85 mg (single dose)	Complete (Jun 2004)	No[e]
009	1	Healthy Subjects	18 (18)	Effects on haloperidol-induced akathisia	7.5 mg haloperidol + placebo or 85 mg PIM (single-dose crossover)	Complete (Jul 2004)	Yes[e]
011	1	Healthy Subjects (aged 40-75)	45 (36)	Polysomnographic assessments and multi-dose PET	0.85, 1.7, 4.3, or 17 mg PIM or placebo (QD for 14 days)	Complete (Dec 2005)	Yes[f]
018	1	Healthy Subjects	252 (132)	Multi-dose, Thorough QT/QTc	17 or 68 mg PIM or placebo or placebo + 400 mg moxifloxacin (moxifloxacin on Day 20 only) (QD for 20 days)	Complete (Dec 2008)	Yes
Subject PD and PD/PD Study Reports							
004	2	PD Dyskinesia	23 (21)	Exploratory efficacy and safety in PD dyskinesia	17 or 51 mg PIM or placebo (single-dose crossover)	Complete (Sep 2006)	No[j]
007	2	Schizophrenia	34 (16)	Effects on haloperidol-induced akathisia	51 mg PIM or placebo (+ stable dose of haloperidol) (once daily for 5 days)	Complete (Aug 2005)	Yes

Abbreviations and footnotes at end of table.

Appendix B, Table 1 Summary of Individual Clinical Studies (Completed and Ongoing) with Pimavanserin (Continued)

Study Suffix (ACP-103-XXX)	Phase	Population	N (n) Randomized (exposed to PIM)	Purpose	Pimavanserin Tartrate Doses (Unless otherwise specified)	Complete[a], Ongoing or Planned	ACADIA Sponsored?
Efficacy and Safety Studies							
Controlled Clinical Studies Pertinent to the Claimed Indication (PD Psychosis)							
006	2	PD psychosis	60 (29)	Placebo-controlled, dose-escalation exploratory efficacy and safety in PD psychosis	17-34-51 mg (escalating) PIM or placebo (QD for 4 weeks)	Complete (Dec 2005)	Yes
012	2b/3	PD psychosis	298 (197)	Placebo-controlled efficacy and safety	8.5 or 34 mg PIM or placebo (QD for 6 weeks)	Complete (Jul 2009)	Yes
014	2b/3	PD psychosis	123 (82)	Placebo-controlled efficacy and safety	8.5 or 17 mg PIM or placebo (QD for 6 weeks)	Stopped Early (Dec 2009)	Yes
020	3	PD psychosis	199 (104)	Placebo-controlled efficacy and safety	34 mg PIM or placebo (QD for 6 weeks)	Complete (Oct 2012)	Yes
Uncontrolled Clinical Studies Pertinent to the Claimed Indication (PD Psychosis) – Subjects Transitioned from Controlled Studies							
010	2	PD/PD Psychosis	N/A (39[g])	Open-label, long-term safety	17-34-51 mg (escalation) PIM (QD)	Complete (May 2013)	Yes
015	3	PD psychosis	N/A (459[h])	Open-label, long-term safety	34 mg PIM fixed dose (QD)	Ongoing (Jul 2007)	Yes
Other Efficacy and Safety Studies in other Subject Populations							
008	2	Schizophrenia	423 (161)	Exploratory efficacy and safety of combination therapy in acute schizophrenia	2 mg risperidone + placebo or 17 mg PIM; 2 mg haloperidol + placebo or 17 mg PIM; 6 mg risperidone alone; (BID for 6 weeks)	Complete (Dec 2006)	Yes
019	2	ADP	212 Planned (~69[i])	Exploratory efficacy and safety in nursing home residents with ADP	34 mg PIM or placebo (QD for 12 weeks)	Ongoing (Mar 2014)	Yes

Abbreviations and footnotes on next page.

Abbreviations: ADME = absorption, distribution, metabolism, and excretion; ADP = Alzheimer's disease psychosis; BID = three times daily; CTA = Clinical Trial Authorisation; IR = Immediate release; N/A = not applicable; PD = Parkinson's disease; PET = positron emission tomography; PIM = pimavanserin; PK = pharmacokinetics; QD = once daily; TID = three times a day

[a] For completed studies the completion date is defined as the last subject's last assessment. For ongoing studies, the date reflects the date of the first subject randomized.

[b] ACADIA sponsorship prior to US IND. Conducted in UK under approved CTA.

[c] 4 Groups: subjects with mild, moderate, or severe hepatic impairment; and healthy subjects.

[d] 3 Groups: subjects with severe renal impairment; subjects with end-stage renal disease; and healthy subjects.

[e] ACADIA sponsorship prior to US IND. Conducted in Sweden under approved CTA.

[f] ACADIA sponsorship prior to US IND. Conducted in France under approved CTA.

[g] 18 of these subjects transitioned from placebo in Study 006 to PIM in Study 010.

[h] 184 of these subjects transitioned from placebo in Study 012, 014, or 020 to PIM in Study 015.

[i] As of 06 January 2016.

[j] Conducted under NIH-sponsored IND.

Appendix B, Table 2 Overview of Placebo-Controlled Studies of Pimavanserin in PD Psychosis with Key Efficacy Results

Study Suffix (ACP-103-XXX) Phase (N)	Region	Dosing Duration (wks)	Study Objectives	Study and Control Dose, Regimen	BPST-PD	Symptom Frequency and Severity at Screening/Baseline	Post-Baseline Visits where Efficacy Assessed	Efficacy Measures (Primary endpoint in bold where applicable)	Primary endpoint rater	Key Efficacy Results[a]
006 Phase 2 (60) (Meltzer et al., 2010)	US	4	Exploratory efficacy, safety	17-34-51 mg (flexible) PBO QD	No	Screening: MMSE ≥21 Baseline: NPI-H+D ≥4	Days 8, 15, 28 (SAPS on Day 28 only)	**UPDRS II+III**, SAPS-H+D, CGI-S, CGI-I, SAPS-H, -D, PPRS	Site-based	UPDRS II+III: Wk 4 LSMΔ = 2.88 (p=0.220) SAPS-H+D Wk 4 LSMΔ = -3.7 (p=0.106)
										(Post hoc: SAPS-PD Wk 4 LSMΔ using mITT population = -3.7 [p=0.023; effect size = 0.61])
012 Phase 3 (298)	US Europe[b] India	6	Efficacy, safety	8.5 mg 34 mg PBO QD	No	Screening: MMSE ≥21 Baseline: NPI-H+D ≥4 SAPS-H+D ≥5	Days 8, 15, 29, 42[d]	**SAPS-H+D**, CGI-S, CGI-I, SAPS-H, -D, CBS, SCOPA-Sleep CBS, NMSS, RUD-Lite, Key 2°: UPDRS II+III	US: Central, indepen-dent Europe, India: Site-based	PIM 34 mg: SAPS-H+D Wk 6 LSMΔ = -0.8 (NSS, effect size = 0.12); US only: SAPS-H+D Wk 6 LSMΔ = -2.5 (NSS, effect size = 0.37); UPDRS II+III: Wk 6 LSMΔ = -0.19 (95% CI: -2.99 to 2.62)
										(Post hoc, US only; PIM 34 mg: SAPS-PD Wk 6 LSMΔ = -2.7 [p<0.050, effect size = 0.44])
014 Phase 3 (123)	US Europe[c]	6	Efficacy, safety	8.5 mg 17 mg PBO QD	No					Terminated early following receipt of 012 data (and because lower doses and same study design used). PIM 17 mg: SAPS-H+D Wk 6 LSMΔ = -2.1 (NSS, effect size=0.32). UPDRS II+III: Wk 6 LSMΔ = -2.1 (95% CI: -5.9 to 1.8)
020 Phase 3 (199) (Cummings et al., 2014)	US Canada	6	Efficacy, safety	34 mg PBO QD	Yes	Screening: MMSE ≥21 Baseline: NPI-H ≥4 or NPI-D ≥4; or NPI-H+D ≥6; SAPS-H or SAPS-D global item (H7 or D13) score ≥3 and a score ≥3 on at least one other non-global item using SAPS-PD	Days 15, 29, 43[d]	**SAPS-PD**, CGI-S, CGI-I, SAPS-H+D, SAPS-H, -D, CBS, SCOPA-Sleep Key 2°: UPDRS II+III	Central, indepen-dent	SAPS-PD Wk 6 LSMΔ = -3.1 (p=0.001, effect size = 0.50); CGI-S Wk 6 LSMΔ = -0.58 (p=0.001, effect size = 0.51); CGI-I Wk 6 LSMΔ = -0.67 (p=0.001, effect size = 0.52); SAPS-H+D Wk 6 LSMΔ = -3.4 (p=0.001, effect size = 0.50); UPDRS II+III: Wk 6 LSMΔ = 0.29 (p=0.814)

Abbreviations: BPST-PD = Brief Psychosocial Therapy – Parkinson's disease; CBS = Caregiver Burden Scale; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression - Severity; D = day; LSMΔ = least squares mean difference; NMSS = Non-Motor Symptoms Score; NSS = not statistically significant; PBO = placebo; PPRS = Parkinson's Psychosis Rating Scale; RUD-Lite = Resource Utilization in Dementia Scale – Lite; SAPS = Scale for the Assessment of Positive Symptoms; SAPS-H+D=SAPS-Hallucinations and SAPS-Delusions subscales; SAPS-PD = SAPS in Parkinson's disease; SCOPA-Sleep = Scales for Outcomes in Parkinson's disease - Sleep; UPDRS II+III = Unified Parkinson's Disease Rating Scale parts II and III; US = United States

[a] For each study efficacy data using the primary analysis method are shown. For 006, 012, and 014 this was analysis of covariance with last observation carried forward (ANCOVA LOCF); for 020 this was mixed-model-repeated-measures with observed cases (MMRM [OC]).

[b] Bulgaria, France, Russia, United Kingdom, and Ukraine.

[c] Austria, Belgium, Italy, Poland, Portugal, Serbia, Spain, Sweden.

[d] Subjects in both the 012 and 020 studies received 42 days (6 weeks) of treatment. The end-of-treatment visit was referred to as Day 42 in 012 and Day 43 in 020.

Appendix B, Table 3 Summary of Pharmacokinetic Data for Pimavanserin Following Multiple Doses in Healthy Subjects

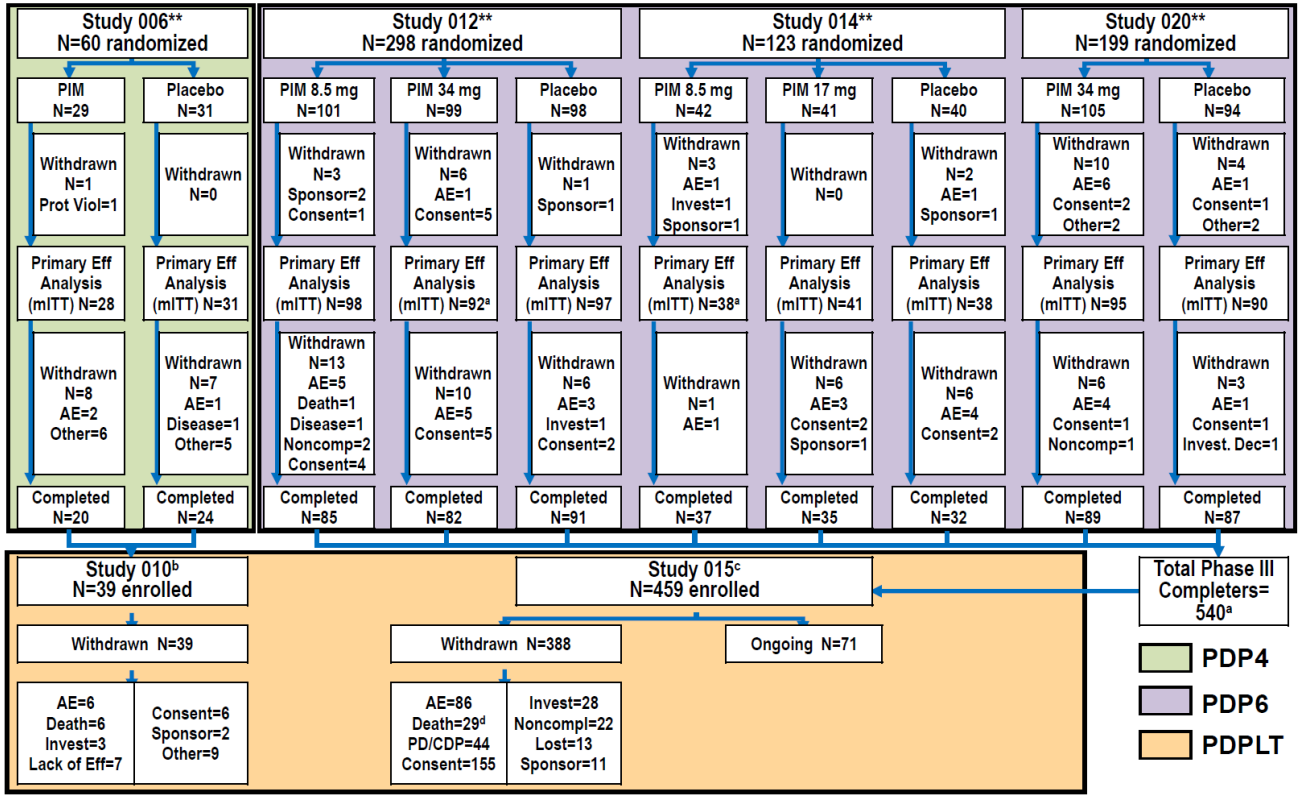
Study Suffix (ACP-103-XXX) (Dosing Schedule) *Population*	Dose [mg] (N)	Day	PK Parameter Mean (SD)						
			C_{max} [ng/mL]	C_t[a] [ng/mL]	t	T_{max} [h] Med (Min, Max)	AUC_{0-24h} [ng-h/mL]	Oral CL/F[b] [L/h]	$t_{1/2}$ [h]
002 (QD × 14 days) *Healthy subjects*	43 (6)	1	21.4 (4.6)			6 (6,9)	379 (81)		
	85 (6)	1	43.2 (5.5)			6 (6,12)	792 (115)		
	128 (6)	1	69.6 (6.6)			6 (6,9)	1250 (143)		
	43 (6)	14	92.9 (31)	60.7 (19)	Predose	6 (6,9)	1839 (681)	25.2 (6.8)	54.6 (19)
	85 (5)	14	193 (28)	120 (19)	Predose	6 (6,9)	3805 (599)	22.8 (3.7)	60.1 (15)
	128 (4)	14	248 (35)	151 (21)	Predose	6 (4,6)	4680 (549)	27.6 (3.3)	48.0 (1.3)
011 (QD × 14 days) *Older healthy subjects*	0.85 (9)	14		1.63 (0.5)	Predose				
	2.1 (9)	14		3.65 (1.1)	Predose				
	4.3 (9)	14		8.52 (2.1)	Predose				
	17 (9)	14		35.0 (10)	Predose				
018 (QD × 20 days) *Healthy subjects*	17 (35)	1	12.1 (5.2)			9 (6,16)	201 (59)		
	68 (38)	1	49.4 (11.3)			9 (6,16)	860 (193)		
	17 (35)	20	46.1 (15.1)			7 (5,12)	849 (284)	10.3 (3.8)	46.5 (14.4)
	68 (38)	20	206 (70.9)			7 (5,10)	3817 (1465)	9.3 (3.6)	54.3 (23.2)

Abbreviations: AUC_{0-24h} = area under the concentration-time curve from time zero to 24 hours; CL/F = oral clearance; C_{max} = maximum observed plasma concentration; h= hours; PK = pharmacokinetic; QD = once daily; SD = standard deviation; T_{max} = time to maximum observed plasma concentration; t = time; $t_{½}$ = terminal plasma half-life

[a] $C_t = C_{min}$ (SD)

[b] CL/F = CLpo

Appendix B, Figure 1 Disposition of Subjects in All PD Psychosis Studies (From Population PDP4 and PDP6: ACP-103-006, ACP-103-012, ACP-103-014, ACP-103-020, APC-103-010, and ACP-103-015)



Abbreviations: AE = adverse events; Prot Viol = protocol violation; PD/CDP = PD or concomitant disease progression; PDP4 = PDP subject analysis population treated with pimavanserin for 4 weeks; Noncompl = noncompliance with the protocol; Consent = subject's voluntary withdrawal of consent; Invest = Investigator decision; Sponsor = Sponsor decision. PDPLT disposition based on Sponsor reclassification

[a] This includes 1 subject each from Study 012 and Study 014 who were excluded from the mITT population due to a missing baseline SAPS score.

[b] One subject enrolled into Study 010 after completing Study 004.

[c] This includes 2 subjects who were screened for Study 020 (but not randomized) and one subject from Study 010. All subjects from Bulgaria and Spain (including 19 completers from Study 012, Bulgaria; 13 completers from 014, Spain) did not have access to Study 015 for regulatory reasons.

[d] This number reflects only the discontinued subjects for whom the reason was specified as death. (There were additional deaths that resulted from AEs but death was not specified as the reason for study discontinuation.)

*Study ACP-103-005 from Population PDP4 is not included in the diagram because the 12 PD subjects enrolled did not necessarily have psychosis.

**Of the randomized subject population in each study, 1 subject did not have a post-baseline efficacy outcome measure in Study 006; 11 and 6 subjects did not have a post-baseline SAPS-H+D value in Studies 012 and 014, respectively; and 14 subjects did not have a post-baseline SAPS-PD value in Study 020; and therefore these subjects were not included in the mITT analysis population in each respective study.

Appendix B, Table 4 Study 015 (Safety Analysis Set)

	Termination Time Frame (N=459)									
	Baseline		Week 2		Week 4		Week 12		All Pre-Week 24	
Termination Reason	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Adverse Event	-	-	14	(3.1)	11	(2.4)	13	(2.8)	38	(8.3)
Death	-	-	-	-	1	(0.2)	-	-	1	(0.2)
Disease Progression	-	-	1	(0.2)	2	(0.4)	5	(1.1)	8	(1.7)
Investigator Decision	-	-	3	(0.7)	3	(0.7)	4	(0.9)	10	(2.2)
Lost to Follow-up	-	-	3	(0.7)	-	-	1	(0.2)	4	(0.9)
Subject Non-Compliance	-	-	-	-	1	(0.2)	-	-	1	(0.2)
Voluntary Withdrawal of Consent	1	(0.2)	13	(2.8)	14	(3.1)	23	(5.0)	51	(11.1)
Any Reason	1	(0.2)	34	(7.4)	32	(7.0)	46	(10.0)	113	(24.6)

Appendix B, Table 5 Treatment-Emergent Adverse Events with Fatal Outcomes by SOC and Preferred Term and by Time Period at Death in the PD/PD Psychosis Open-label Long-term Studies (Population PDPLT: ACP-103-010 and ACP-103-015)

System Organ Class Preferred Term	First 4 weeks (N=498)[a] n(%)	1 - 3 months (N=498) n(%)	>3 - 6 months (N=413) n(%)	>6 - 12 months (N=361) n(%)	>1 - 2 years (N=291) n(%)	>2 - 3 years (N=177) n(%)	>3 - 4 years (N=119) n(%)	>4 years (N=70) n(%)	PIM (N=498) n(%)
Overall	**0 (0.0)**	**3 (0.6)**	**5 (1.2)**	**9 (2.5)**	**23 (7.9)**	**5 (2.8)**	**8 (6.7)**	**6 (8.6)**	**59 (11.8)**
Cardiac disorders	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**	**2 (0.6)**	**10 (3.4)**	**1 (0.6)**	**3 (2.5)**	**2 (2.9)**	**20 (4.0)**
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	2 (1.7)	1 (1.4)	5 (1.0)
Cardiac arrest	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	1 (0.8)	0 (0.0)	3 (0.6)
Acute myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.6)	0 (0.0)	0 (0.0)	2 (0.4)
Cardio-respiratory arrest	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	2 (0.4)
Cardiopulmonary failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
Cardiac failure congestive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Cardiomyopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Myocardial ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**	**3 (0.8)**	**5 (1.7)**	**2 (1.1)**	**0 (0.0)**	**0 (0.0)**	**12 (2.4)**
Acute respiratory failure	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)
Pneumonia aspiration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.6)	0 (0.0)	0 (0.0)	3 (0.6)
Aspiration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.6)	0 (0.0)	0 (0.0)	2 (0.4)
Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pulmonary haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Nervous system disorders	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**	**1 (0.3)**	**4 (1.4)**	**0 (0.0)**	**2 (1.7)**	**1 (1.4)**	**10 (2.0)**
Parkinson's disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	1 (1.4)	3 (0.6)
Cerebrovascular accident	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
Dementia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.4)
Cerebral haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Haemorrhagic stroke	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Parkinsonism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Infections and infestations	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**3 (1.0)**	**0 (0.0)**	**1 (0.8)**	**2 (2.9)**	**7 (1.4)**
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	1 (0.8)	1 (1.4)	4 (0.8)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.2)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Urosepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

Appendix B, Table 5 Treatment-Emergent Adverse Events with Fatal Outcomes by SOC and Preferred Term and by Time Period at Death in the PD/PD Psychosis Open-label Long-term Studies (Population PDPLT: ACP-103-010 and ACP-103-015), continued

System Organ Class Preferred Term	First 4 weeks (N=498)a n(%)	1 - 3 months (N=498) n(%)	>3 - 6 months (N=413) n(%)	>6 - 12 months (N=361) n(%)	>1 - 2 years (N=291) n(%)	>2 - 3 years (N=177) n(%)	>3 - 4 years (N=119) n(%)	>4 years (N=70) n(%)	PIM (N=498) n(%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (0.7)**	**0 (0.0)**	**1 (0.8)**	**1 (1.4)**	**4 (0.8)**
Brain neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Colon cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Hepatic neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Recurrent cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.2)
Vascular disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**	**1 (0.3)**	**0 (0.0)**	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**3 (0.6)**
Aortic aneurysm	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Aortic dissection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Circulatory collapse	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
General disorders and administration site conditions	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**	**1 (0.8)**	**0 (0.0)**	**2 (0.4)**
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.4)
Gastrointestinal disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**
Gastrointestinal haemorrhage	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Injury, poisoning and procedural complications	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**
Subdural haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.2)**
Rhabdomyolysis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

MedDRA version 15.1 was used to categorize the adverse events.

A Treatment-Emergent Adverse Event (TEAE) was defined as an adverse event that occurred on or after the administration of first study drug dose and before or on last dose date +30 days.

A subject may have more than one TEAE per system organ class (or preferred term); in such case, this subject is counted only once per system organ class (or preferred term) per time period.

[a] The denominator for a time period is the number of subjects on treatment (including a 30-day follow-up) during that particular time period.

Appendix C Major Entry Criteria for Study 020

Inclusion Criteria

1. Male/female, 40 years of age or older with a clinical diagnosis of idiopathic Parkinson's disease (PD) with a minimum duration of 1 year
2. Presence of visual and/or auditory hallucinations, and/or delusions, occurring during the 4 weeks prior to study screening
3. Psychotic symptoms must have developed after PD diagnosis
4. Symptoms severe enough to warrant treatment with an antipsychotic agent as documented by items A and B of the NPI, and defined a score of ≥4 on either the hallucinations (frequency × severity) or delusions (frequency × severity) scales of the NPI or a total NPI-H+D score ≥6 at screening
5. Subjects that are on anti-Parkinson's medication must be on a stable dose for 1 month prior to Study Day 1 (Baseline) and during the trial
6. Subject that has received stereotaxic surgery for subthalamic nucleus deep brain stimulation must be at least 6 months post-surgery and the stimulator settings must have been stable for at least 1 month prior to Study Day 1 (Baseline) and must remain stable during the trial
7. The subject is willing and able to provide consent
8. Caregiver is willing and able to accompany the subject to all visits
9. Subject and caregiver are willing and able to adequately communicate in English for the purposes of the primary assessment

Exclusion Criteria

1. Subject has a history of significant psychotic disorders prior to or concomitantly with the diagnosis of Parkinson's disease including, but not limited to, schizophrenia or bipolar disorder
2. Subject has received previous ablative stereotaxic surgery (i.e., pallidotomy and thalamotomy) to treat Parkinson's disease
3. Was using any medication prohibited or restricted, including other antipsychotic medication
4. Subject has current evidence of a serious and or unstable cardiovascular, respiratory, gastrointestinal, renal, hematologic or other medical disorder
5. Subject has had a myocardial infarction in last 6 months
6. Subject has any surgery planned during the screening, treatment or follow-up periods

Appendix D Development of the Scale for the Assessment of Positive Symptoms in Parkinson's Disease (SAPS-PD)

The SAPS was originally developed for schizophrenia but was adapted for use in early PD psychosis studies by using the combined score of the hallucinations (H) and delusions (D) domains (SAPS-H+D). This was the primary measure of efficacy in earlier international Phase 2b/3 Studies 012 and 014. SAPS-H+D selection was based principally on the relevance of the selected domains to the positive symptoms of PD psychosis, their high inter-rater reliability, and their utility for assessing effects of treatment on the frequency and severity of hallucinations and delusions in PD psychosis subjects. The SAPS also had precedence in the US Parkinson Study Group (US PSG) trial of clozapine, which is the only atypical antipsychotic that has shown efficacy in placebo-controlled PD psychosis trials (Pollak et al., 2004; US PSG, 1999).

In parallel with the early Phase 2b/3 program for pimavanserin, ACADIA conducted a number of analyses to further characterize the utility of the SAPS-H+D in PD psychosis. Analyses were conducted to evaluate the factor structure of the SAPS-H+D domains (20 items) and to further elucidate which individual items of the scale are most reflective of PD psychosis symptomatology. The analyses were conducted using baseline (pre-treatment) data from pimavanserin Studies 006, 012, and 014 (N=481), and from the US Parkinson's study group clozapine database (N=60; US PSG, 1999). SAPS-H+D items were selected if they consistently achieved at least a 10% threshold for moderate to severe symptom expression (based on the entire pooled dataset from all four trials), similar to the >10% threshold used in factor analyses of the SAPS and Scale for the Assessment of Negative Symptoms in schizophrenia (Liddle 1987; Toomey 1997).

These data led to establishment of Scale for the Assessment of Positive Symptoms in Parkinson's Disease (SAPS-PD) as the primary endpoint in pivotal Study 020. While subjects were interviewed using the full 20-item SAPS-H+D scale (as a supportive endpoint), the primary analysis was the sum of responses on the subset of items reflective of the symptoms expressed in PD psychosis. This select subset was defined SAPS-PD (Table 8–6). The SAPS-PD measure (Voss et al., 2013) thus became the measurement of choice for evaluation of psychotic symptoms in this patient population.

Appendix E Narratives of Subject Deaths in Short-Term Controlled Studies

SUBJECTS TREATED WITH PIMAVANSERIN 8.5 MG WHO DIED DURING THE STUDY

Study No. ACP-103-012
Subject 005005

Narrative Type: SAE that resulted in discontinuation and Death

Treatment Group: pimavanserin 8.5 mg

Event: Myocardial infarction

Subject 005005, a 61-year-old white male, had a relevant medical history of Parkinson's disease (Dec 2001) with visual hallucinations and delusions (both since May 2007), low WBC count (May 2008), abdominal pain (Feb 2007), and elevated potassium (May 2008). Subject was receiving Sinemet 10/100 (carbidopa 10 mg and levodopa 100 mg) daily (29 Jun 2006) and Stalevo 150 (carbidopa 37.5 mg, levodopa 150 mg, and entacapone 200 mg) every 3 hours (Apr 2003) for Parkinson's disease (no change within 6 months of study entry). Subject had no history of cardiovascular disease and ECG overall interpretation was normal at all study visits. Subject ingested the first dose of pimavanserin 8.5 mg (study drug) on Day 1 ((b) (6)). On Day 38, TEAE of increased blood creatine phosphokinase (CPK) (mild, not related, and ongoing at time of death) was reported with abnormally high CPK value of 208 U/L (vs. 106 U/L at baseline; reference range: 0-174 U/L) and abnormally low WBC count value of 3.3×10^9 L (vs. 2.9×10^9 L at baseline; reference range: 4.5-11.0 $\times 10^9$ L). Blood pressure was 118/66 mmHg (supine) and 120/68 mmHg (standing), pulse was 54 bpm (supine) and 60 bpm (standing), respiration 14 breaths per minute, and temperature 97.5°F (36.4°C). Since the subject was asymptomatic, the subject continued to be followed and treated with study drug. On Day 46, the subject did not answer the door at his home. Police were called and the subject was found dead in bed. There were no signs of overdose, suffocation, or trauma. The subject's son called to inform the study site that the subject had deceased. The certificate of death listed the date of death as (b) (6) (Day 46) at 07:00 hours. On that day, TEAE of myocardial infarction (severe, unlikely related, with an outcome of death) was recorded that resulted in discontinuation of study drug (last dose on Day 46); no additional TEAEs were recorded. The immediate cause of death was listed as probable myocardial infarction with a secondary cause listed as Parkinson's disease. No additional information is available.

SUBJECTS TREATED WITH PIMAVANSERIN 34 MG WHO DIED DURING THE STUDY

Study No. ACP-103-012
Subject 118001

Narrative Type: SAE that resulted in discontinuation and Death

Treatment Group: pimavanserin 34 mg

Event: Respiratory distress

Subject 118001, an 84-year-old white female, had a relevant medical history of Parkinson's disease (2001) with visual hallucinations (Feb 2008) and depressive syndrome (date unknown). Subject was receiving Sinemet 100 (carbidopa 25 mg/levodopa 100 mg) every 8 hours (18 Sept 2008) for Parkinson's disease (change within 6 months of study entry due to psychosis) and fludrocortisones 0.3 mg daily for orthostatic hypotension and syncope (29 Sept 2009). On Day -28 ([redacted]), subject was hospitalized with syncope and discharged on Day -21 ([redacted]).

Subject ingested the first dose of pimavanserin 34 mg (study drug) on Day 1 ([redacted]). On Day 32 (3 days post-last dose), the subject was hospitalized with a serious TEAE of respiratory distress (severe and unlikely related) following cataract surgery (see table below). Respiratory distress resulted in discontinuation of study drug (last dose on Day 29). Post-operatively, the subject was fatigued with a normal neurological examination and a Glasgow score of 13. Hematology results revealed hyperleukocytosis (unspecified), and a temperature of 38.8°C (101.8°F).

On Day 33, hepatic tests and blood ionogram (sodium, potassium, and chloride) were reported as normal. On Day 34, subject had hypoventilation of the right lung and was started on oxygen and unspecified antibiotics. On Day 36, Glasgow score was 13, chest x-ray revealed left lung atelectasis, and subject was intubated. On Day 39 (19 days post-last dose), subject was hypokalemic (potassium concentration 2.6 mmol/L).

On Day 43, blood pressure was 110/60 mmHg and hemoglobin was 9.5 g/dL. Subject was described as calm and less vigilant, enteral feeding was initiated. On Day 49, a tracheotomy was performed. On Day 56, sinus tachycardia (rate not provided) was noted. Subject's respiratory status continued to decline and subject died on Day 61 ([redacted]) (32 days post-last dose). No additional information is available.

Subject 118001 in the 34 mg group (ACP-103-012)							
Study Day	**Creatinine**	**Hemoglobin g/dL**	**PO_2 mmHg**	**PCO_2 mmHg**	**Glasgow score**	**Temperature**	**Potassium mmol/L**
Day 32	--	--	--	--	13	38.8°C/101.8°F	--
Day 33	--	--	--	--	15	---	--
Day 35	normal	10.6	74	74		--	--
Day 36	normal	10.0	70	90	13		--
Day 37	normal	10.5			--	--	--
Day 38		9.2	--	--	--	37.8°C/100.0°F	--
Day 39	normal	10.0	--	--	--	--	2.6
Day 40	--	9.6	--	--	--	--	--
Day 43	--	9.5	--	--	--	--	--
Day 44	--		200	52	--	37.2°C/98.9°F	--
Day 49	normal	9.0	--	--	--	--	--
Day 51	normal	9.6	--	--	--	--	--
Day 52	--	9.5	65		--	--	--
Day 53	normal	--	--	--	--	38.5°C/101.3°F	--
Day 55		8.5	--	--	--	--	--
Day 56	--	--	158	70	--	--	--
Day 58	--	--	--	--	14	38.0°C/100.4°F	--
Day 60	--	--	--	--	--	--	--
Day 61	--	10.0	--	--	13	--	--

Study No. ACP-103-020
Subject 001-101

Narrative Type: serious TEAE resulting in study drug discontinuation; serious TEAEs; serious TEAE with outcome of death

Treatment Group: pimavanserin 34 mg

Events: psychotic disorder (serious TEAE resulting in study drug discontinuation); sleep disorder (serious TEAE); multi-organ failure (serious TEAE); septic shock (serious TEAE with outcome of death)

Subject 001-101, a 76-year-old white male, had a relevant medical history of PD since September 2006 with visual hallucinations and delusions since 13 Sep 2010, treated with rasagiline 1 mg daily (14 Oct 2010), Stalevo 150 (carbidopa 37.5 mg/levodopa 150 mg/ entacapone 200 mg) every 4 hours (14 Oct 2010), rivastigmine patch 9.5 mg daily (14 Oct 2010), and Sinemet 25/100 (carbidopa 25 mg/levodopa 100 mg), one-half tablet BID (17 Nov 2010).

The subject also had hypertension since 2005, treated with fosinopril 40 mg daily (16 Jun 2009), gastroesophageal reflux disease since 2000, treated with omeprazole 20 mg daily (14 Jul 2009), polyneuropathy since 2005, and obstructive sleep apnea since Feb 2009.

He had a screening MMSE score of 21 and baseline SAPS scores of 7 (SAPS-PD), 7 (SAPS-H), 0 (SAPS-D), and 7 (SAPS-H+D).

The subject took the first dose of study drug (pimavanserin 34 mg) on (b) (6) (Study Day 1).

On (b) (6) (Study Day 4) the subject was restless and confused and had an altered sleep pattern, and was hospitalized due to serious events of psychotic disorder (CRF term, worsening of psychosis) and sleep disorder (CRF term, worsening of sleep disorder). Both events were severe and not related to study drug, and both were ongoing at death. Trazodone 50 mg was prescribed for sleep disorder. According to the subject's family, he was confusing day and night and had become very psychotic. Diagnostic assessments to rule out other causes of acute confusion were negative.

On (b) (6) (Study Day 7) the subject was discharged to a nursing home because his wife was unable to care for him at home.

The subject's condition did not improve, and he had a low-grade fever. On (b) (6) (Study Day 9) study drug was discontinued due to psychotic disorder, and the subject's condition remained unchanged during the day. Clozapine 25 mg was begun for psychotic disorder, and trazodone 25 mg for sleep was discontinued.

In the evening of (b) (6) the subject was hospitalized due to continued worsening of his general condition and clinical evidence of septic shock, including decreased consciousness, fever, and hypotension. Leukocytosis and acute renal failure were noted, and a chest x-ray suggested aspiration pneumonia; the subject was treated accordingly.

A chest x-ray revealed a pleural effusion and peribronchial thickening compatible with bronchitis, and mildly prominent bibasilar lung markings compatible with mild bibasilar atelectasis or pneumonia. An ECG showed sinus tachycardia with a heart rate of 123 bpm, left axis deviation, and right bundle branch block, with no evidence of ischemia or acute injury.

The subject's condition remained critical, and medical treatment was discontinued. The subject was provided with comfort measures only, in accordance with the family's request.

On (b) (6) (Study Day 10) the subject remained in critical condition, and he was transferred to hospice care. The subject died in the evening of (b) (6) due to the serious event of multi-organ failure (severe; not related to study drug; ongoing at death) caused by septic shock (severe; unlikely related to study drug). The cause of death was listed as septic shock. No autopsy was performed.

Study No. ACP-103-020
Subject 303-121

Narrative Type: serious TEAE resulting in discontinuation of study drug; serious TEAE with outcome of death

Treatment Group: pimavanserin 34 mg

Events: psychotic disorder (serious TEAE resulting in discontinuation of study drug); sepsis (serious TEAE with outcome of death)

Subject 303-121, a 74-year-old white male, had a relevant medical history of PD since June 2005 with visual hallucinations and delusions since Dec 2011 and auditory hallucinations since May 2012, treated with rasagiline 0.5 mg daily (09 Jun 2009), Sinemet 25/100 CR (carbidopa 25 mg/levodopa 100 mg) two tablets daily (08 Dec 2009), and Sinemet 25/100 (carbidopa 25 mg/levodopa 100 mg) 5.5 tablets daily (27 Sep 2010).

The subject also had dementia and memory loss since Jun 2011, treated with donepezil 10 mg daily (16 Dec 2011), hyperlipidemia since 2010, treated with simvastatin 20 mg daily (2010), dermatitis since May 2011, and borderline left ventricular hypertrophy and hyperdynamic left ventricular diastolic dysfunction since 2012. He was taking aspirin 81 mg daily for cardiac prophylaxis (2010). The subject had a screening MMSE score of 28 and baseline SAPS scores of 12 (SAPS-PD), 9 (SAPS-H), 3 (SAPS-D), and 12 (SAPS-H+D).

The subject took the first dose of study drug (pimavanserin 34 mg) on (b) (6) (Study Day 1).

At baseline, an intermittent rash was noted that had reportedly been present for about a year, and was diagnosed as dermatitis by a dermatologist. The subject's baseline white blood cell count was slightly elevated (12.7×10^9/L) (reference range 4.5-11 $\times 10^9$/L) with 29% eosinophils (reference range 0-4.5 $\times 10^9$/L) on (b) (6) (Study Day -14) (a baseline eosinophil count was not available). There were no clinical signs of infection.

On (b) (6) (Study Day 8) the subject experienced hallucination (moderate; not related to study drug; ongoing at death).

On (b) (6) (Study Day 15) the subject's white blood cell count was 14.0×10^9/L, and eosinophils were 41.1%.

On (b) (6) (Study Days 16-21) the subject received methylprednisolone three tablets daily for dermatitis.

On (b) (6) (Study Day 29) the subject's white blood cell count was 13.6×10^9/L and eosinophils were 40.9%.

On [redacted] (Study Day 38) the subject was taken to the emergency room with altered mental status (increased hallucinations; delusional and paranoid) and bilateral lower extremity edema, and was admitted to the hospital on [redacted] (Study Day 39). All test results, including white blood cell count, chest x-ray, brain CT, and urinalysis, were normal. A serious TEAE of psychotic disorder was recorded (severe; possibly related to study drug; ongoing at death) that resulted in study drug discontinuation (last dose [redacted] Additional TEAEs on [redacted] were confusional state (severe; possibly related to study drug; ongoing) and agitation (severe; not related to study drug; ongoing), that were treated with a single IM dose of haloperidol 2 mg on [redacted] (Study Day 41). The physician felt that the condition was due to fluctuation of the subject's underlying PD.

On physical examination there were no cardiac murmurs or gallops, and the subject's chest was bilaterally clear to auscultation. Bilateral edema (+2) above the ankle was noted and was treated with IV furosemide 20 mg once daily on [redacted] and [redacted] (Study Days 39 and 40) and oral furosemide 20 mg on [redacted] (Study Day 41).

On [redacted] the subject was scheduled for discharge, but his condition markedly worsened, and he became more combative and delirious, with bilateral pneumonia and a urinary tract infection. Blood cultures were positive, with systemic sepsis, and antibiotics were started, but were withdrawn following further consultation with the subject's family. The subject gradually became unresponsive.

Rasagiline was increased to 1 mg daily on [redacted] but was decreased to 0.5 mg on [redacted] On [redacted] aspirin, simvastatin, and donepezil were discontinued.

On [redacted] (Study Days 41-43), IV sodium chloride 0.45%, 1000 mL, was administered. On [redacted], (Study Days 42-43), IV sodium chloride 0.9%, 1000 mL, was also administered.

On [redacted] a serious TEAE of sepsis (severe; not related to study drug) was documented and confirmed by laboratory results obtained on [redacted] (Study Day 40). Vancomycin 1200 mg IV was administered for sepsis, but was discontinued on [redacted] (Study Day 43) due to worsening renal function.

On [redacted] the subject showed signs of pneumonia, including bilateral crackles. A chest x-ray was performed and aspiration pneumonia (severe; not related to study drug) was diagnosed. The subject's blood pressure was 73/47 mmHg, heart rate was 109 bpm, and temperature was 102.7°F. Rectal paracetamol 650 mg was given for sepsis fever. Blood cultures revealed gram-positive cocci, and urinalysis was positive for nitrites, 50-100 red blood cells/hpf (reference range 0-2/hpf) and 5-10 white blood cells/hpf (reference range

0-3/hpf). Blood and urine cultures grew *Staphylococcus aureus*. Urinary tract infection (severe; not related to study drug) was documented.

Sepsis, urinary tract infection, and bilateral aspiration pneumonia were treated with Zosyn® (piperacillin/tazobactam) 3.375 g TID IV, and Zyvox® (linezolid), 300 mg BID IV. Following further consultation with the subject's family, comfort care measures were instituted.

On (b) (6) (Study Day 44), the subject's status continued to decline; blood pressure was 70/40 mmHg, heart rate was reported as tachycardic, and temperature was 104°F. Oral furosemide 20 mg daily was administered for bilateral lower extremity edema.

On (b) (6) (Study Day 45) the subject died due to the serious event of sepsis (severe; not related to study drug). The death certificate identified the cause of death as sepsis secondary to bilateral aspiration pneumonia and urinary tract infection. No autopsy was performed, and no additional information is available.

SUBJECTS TREATED WITH PLACEBO WHO DIED DURING THE STUDY

Study No. ACP-103-020
Subject 028-101

Narrative Type: serious TEAE resulting in discontinuation of study drug and death

Treatment Group: placebo

Events: transient ischemic attack (serious TEAE); arrhythmia (serious TEAE resulting in discontinuation of study drug); cardio-respiratory arrest (death)

Subject 028-101, an 85-year-old white male, had a relevant medical history of PD since Sep 2002 with visual hallucinations and delusions since Mar 2010, treated with Sinemet (carbidopa/levodopa), one capsule every 3 hours (30 Jun 2010), and memory loss secondary to PD, treated with rivastigmine, 9.5 mg patch daily (08 Mar 2010).

The subject also had hypertension since 2002, valvulopathy since Jan 2007, atrial fibrillation since Oct 2010, treated with aspirin 81 mg daily (24 Oct 2005), hypothyroidism since 2008, treated with levothyroxine 50 µg daily(2008), osteoarthritis since 1980, and dyspnea since Mar 2005. The subject had a screening MMSE score of 21 and baseline SAPS scores of 9 (SAPS-PD), 9 (SAPS-H), 0 (SAPS-D), and 9 (SAPS-H+D).

The subject took the first dose of study drug (placebo) on (b) (6) (Study Day 1).

On [redacted] (Study Day 13) the subject was hospitalized for acute onset of change in mentation. The subject had a 10-minute episode of unresponsiveness without loss of consciousness, which resolved before his arrival at the hospital and was attributed to a serious TEAE of transient ischemic attack (moderate; unlikely related to study drug; resolved the same day with no sequelae).

An EEG was abnormal due to generalized slowing of background activity consistent with diffuse cerebral dysfunction, which could have indicated toxic, metabolic, or neurodegenerative encephalopathy. An ECG revealed atrial fibrillation (present at screening) with a ventricular rate of 57 bpm; aspirin 81 mg daily was continued (the subject was not a good candidate for anticoagulation with Coumadin® due to confusion and possible frequent falls). A cardiac consultation considered the possibility of an embolic episode secondary to underlying atrial fibrillation. Laboratory test results were generally within normal reference ranges. Cardiac troponin was 0.10 ng/mL (reference range 0.04-0.77 ng/mL). A serious event of arrhythmia (preferred term, cardiac dysrhythmia) was documented (severe and unlikely related to study drug). From [redacted] (Study Days 16-36), the subject received a daily 0.2 mg nitroglycerin patch for cardiac arrhythmia prophylaxis.

A chest x-ray showed volume loss involving the right hemithorax with segmental atelectasis of the right middle lobe and subsegmental atelectasis of the right lower lobe, suggesting a post-obstructive process. A right pleural effusion was also noted. A chest CT scan showed moderate bilateral pleural effusions, areas of airspace consolidation in the right lower lobe and right middle lobe suggesting round atelectasis, cardiomegaly, coronary arterial calcifications, and mild aneurysmal dilation of the ascending thoracic aorta. Bronchodilators were begun.

A brain CT scan showed white matter disease suggesting chronic microangiopathy, with no evidence of acute intracranial pathology. Non-serious TEAEs were documented, including sinusitis (mild; unlikely related to study drug; resolved [redacted] [Study Day 16]), urinary tract infection (*Klebsiella pneumoniae* and *Escherichia coli* reported in the urine culture) (mild; unlikely related to study drug; resolved [redacted] [Study Day 23]), pleural effusion (mild; unlikely related to study drug; resolved [redacted] [Study Day 23]) and aspiration pneumonia (severe; unlikely related to study drug; ongoing). The following were initiated: ceftriaxone 1 gram IV daily for urinary tract infection, sinusitis, and bilateral pleural effusion; cefuroxime 500 mg BID and intranasal albuterol for pneumonia; and amlodipine 5 mg daily for hypertension.

On [redacted] (Study Day 14), a carotid Doppler ultrasound showed no evidence for hemodynamically significant stenosis involving either carotid system. An MRI brain scan showed diffuse small vessel ischemic changes and parenchymal volume loss, and opacity of

the right maxillary and ethmoid sinuses likely to indicate sinusitis. There was no evidence of an acute infarct or mass effect. An echocardiogram showed an ejection fraction of 50 to 55% with severe aortic valvular stenosis, moderate aortic regurgitation, and tricuspid regurgitation with mild pulmonary hypertension.

On (b) (6) (Study Day 16), swallow assessment with video was performed and dysphagia (CRF term, pharyngeal dysphagia) (moderate; unlikely related to study drug; ongoing) was noted. Dysphagia was treated with diet change and thickened liquids.

On (b) (6) the subject was transferred to an acute rehabilitation facility in improved condition. The admission diagnosis was exacerbation of PD with psychosis, dysphagia, dysarthria, encephalopathy, transient ischemic attack, mild dementia, atrial fibrillation, urinary tract infection, chronic plural effusions, and hypertension. Medications included amlodipine 5 mg daily for hypertension, cefuroxime 500 mg BID for 7 days for pneumonia, levothyroxine 50 µg daily for thyroid replacement, aspirin 81 mg daily, carbidopa/levodopa, one capsule every 3 hours, nitroglycerin patch 0.2 mg daily for cardiac arrhythmia prophylaxis, rivastigmine patch 9.5 mg daily, albuterol inhaler for pneumonia, *Lactobacillus acidophilus*, one tablet BID, for general health, and study drug (placebo). The subject's rehabilitation program included daily physical, occupational, and speech therapy. On Day 17, an ECG revealed atrial fibrillation with a ventricular rate of 62 bpm.

On (b) (6) (Study Day 27) (day of last dose), study drug was discontinued due to arrhythmia, which was ongoing at the time of the subject's death.

On (b) (6) (Study Day 33) the subject had an episode of mild epistaxis not associated with headache or increased blood pressure. Vital signs were blood pressure 117/68 mmHg and pulse rate 65 bpm, and treatment included nasal packing.

On (b) (6) (Study Day 34) no further epistaxis was noted; the subject's blood pressure was 112/67 mmHg. On (b) (6) (Study Day 35) the subject's blood pressure was 109/69 mmHg, and amlodipine 5 mg daily was held. The subject was doing well with rehabilitation, and discharge was planned for (b) (6)

On (b) (6) (Study Day 36) (9 days post last dose of study drug), the subject's blood pressure was 132/82 mmHg, and amlodipine 5 mg daily was discontinued. While having occupational therapy, the subject collapsed suddenly and was noted to be in cardiac arrest. Resuscitation was attempted but the subject died; no autopsy was performed. Death was due to a serious TEAE of cardio-respiratory arrest (severe; unlikely related to study drug).